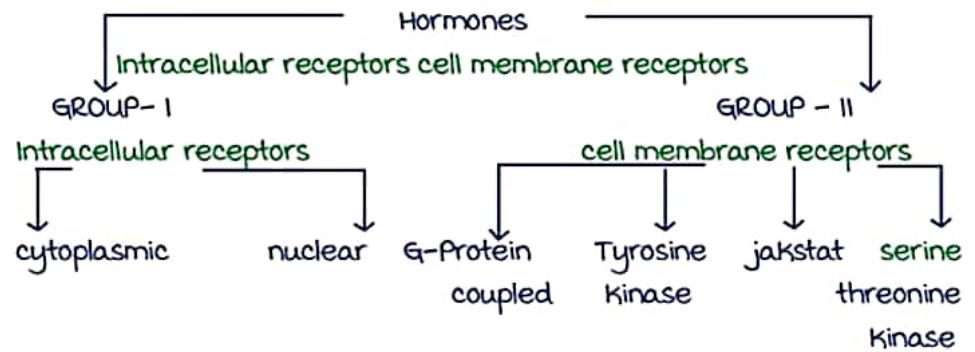
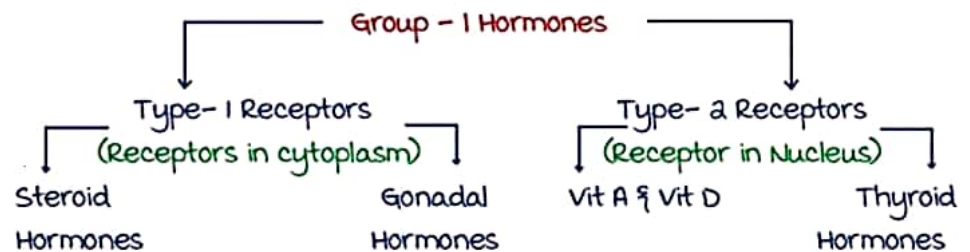




Group - I hormones

00:10:24

- Steroid hormones
- Gonadal hormones
- Vit A & Vit D
- Thyroid hormones



Steroids receptor is bound to Heat shock protein (HSP) in the resting state

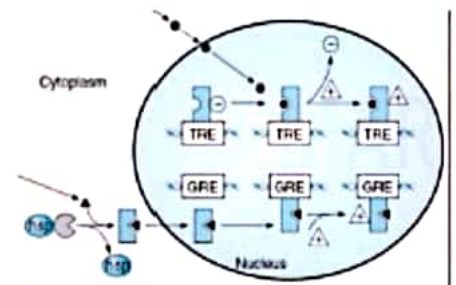
Dissociation of HSP conformational change in receptor when Ligand binds to receptor

Receptor with Ligand moves into the nucleus & binds to GRE (Glucocorticoid Responsive elements) → Protein translation

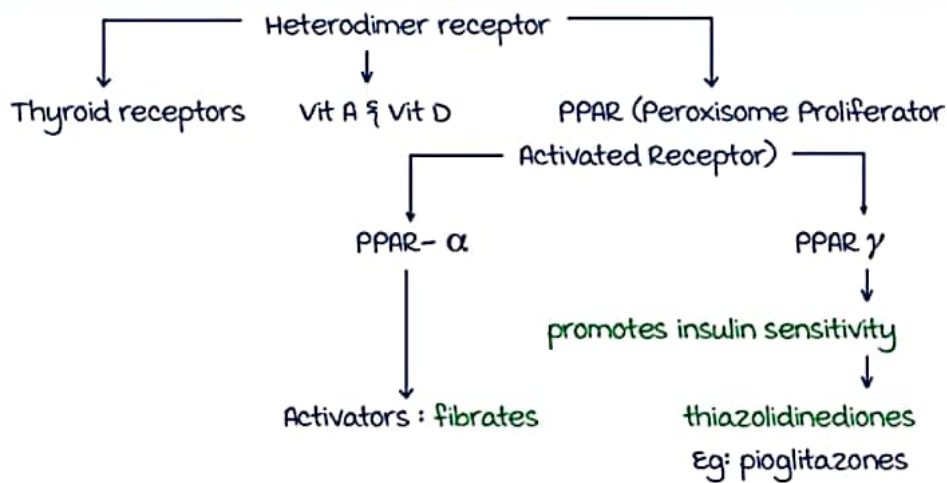
- Thyroid receptors are located inside the nucleus

Binds to TRE (Thyroid Responsive Elements)

Protein translation



- Steroid receptors - Homodimer receptors - co activator binding
- Thyroid receptors - heterodimer receptors - co repressor
Inhibition followed by coactivator binding



Orphan receptors

00:18:43

- Orphan receptors are "Constitutively activated"
- Eg:
 - SF-1 } Required for Gonadotrope cell growth, they are actually
 - DAX-1 } transcription factors.
- HNF-4 α - also transcription factors
 - mutation produces MODY- Type I (maturity onset DM in young)

Group- II hormones

00:20:46

- They have got receptors in the cell membrane

1. GPCR : [G- Protein Coupled Receptors]

- They have Seven membrane Spanning domains - α, β, γ, complex bound to GDP.

↓
(In resting state)

when hormone comes and binds, there will be change in the configuration.

↓
GDP → GTP

α- GTP dissociates and bind to effectors.

effector = 2nd messenger
(cAMP, IP3/ DAG, cGMP)

cAMP- Gs or Gi

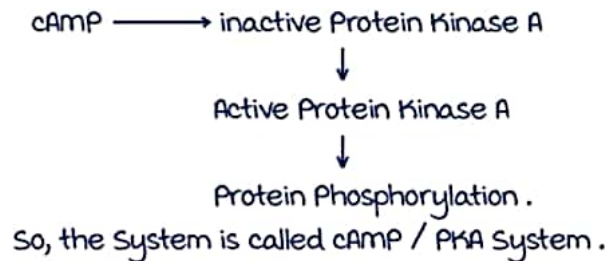
IP3/ DAG - Gq

cGMP - Gt (transducin)

Hormones acting via cGMP :

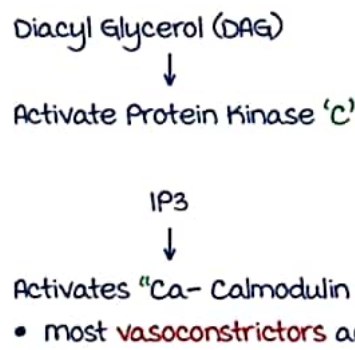
- Vasodilators act via cGMP.
- Eg: NO, ANF (Atrial Natriuretic Factor)

Hormones acting via cAMP :



hormone acting via IP3/ DAG system :

Phosphoinositol pyrophosphate (PIP₂) $\xrightarrow{\text{Phospholipase C}}$ Diacyl Glycerol (DAG) + Inositol triphosphate (IP₃)



Hormones acting via cAMP & IP₃/ DAG pathway

00:27:24

	cAMP (G _i)	IP ₃ /DAG
• Hypothalamus	CRH	TRH, GnRH
• Pituitary (Anterior)	ACTH, FSH, LH	v 1 Oxytocin
	TH + V _a /V ₃	
• Vasoconstrictors		AT-II, substance P
• Pancreas	Glucagon, Somatostatin (G _i)	
• G.I.T	Secretin	cCK, Gastrin .
• ANS	Alpha 2 (G _i), Beta	Alpha 1, Muscarinic Ach
• miscellaneous	PTH, Calcitonin	

most potent vasoconstrictor in the human body - wotensin

$\alpha_a, \beta_1, \beta_2, \beta_3$ - act via cAMP

α_1, α_2 - acts via IP₃/DAG

- All the hormones mentioned above under cAMP are G_s (G -stimulatory) hormones, that means they increase cAMP.
- Example of G_i Hormone - somatostatin & α_s Receptors - they decrease cAMP.

b tyrosine kinase

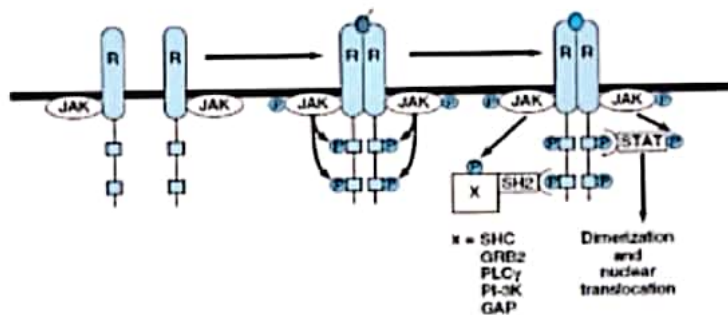
c Janus kinase (JAK)

} Both exists as monomers

Once the hormones come and binds, there will be intracellular dimerisation.

Then, the protein gets phosphorylated either Tyr. Kinase/ Janus Kinase

Translocated to nucleus.



Hormones acting via Thyrosine kinase, JAK-STAT & Serine kinase

00:33:55

Tyrosine Kinase

- Insulin
- EGF (Epidermal)
- IGF (Insulin)
- NGF (Nerve)
- PDGF (Platelet derived)
- FGF (Fibroblast)
- All Growth Factors (GF)

act via Tyr. Kinase except TGF α & β

JAK-STAT

- GH
- prolactin
- EPO (Erythropoietin)

serine Kinase

- TGF (Transformation GF)
- Activin
- inhibin
- BMP (Bone morphogenic Protein)

Active space

- most potent fibrogenic cytokine in the human body "TGF β "
- GH & prolactin are together called as twin hormones.

ANTERIOR PITUITARY

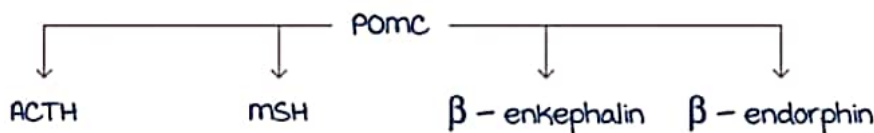
Introduction

00:00:27

- Anterior pituitary is the master gland of endocrine
- CD₄ + T cells are the important components of immune system

Hormones produced by the anterior pituitary :

- 6 hormones are produced by the anterior pituitary
 - a. Prolactin - Produced by lactotrophs
 - b. Growth hormone - Produced by somatotrophs
 - c. LH/FSH - Produced by gonadotrophs
 - d. TSH - Produced by thyrotrophs
 - e. POMC - Produced by corticotrophs
- First cells to develop in the anterior pituitary at 6 weeks of gestation are the corticotrophs, they produce POMC (Pro Opio melanocorticotrophic hormone) - has 4 derivatives

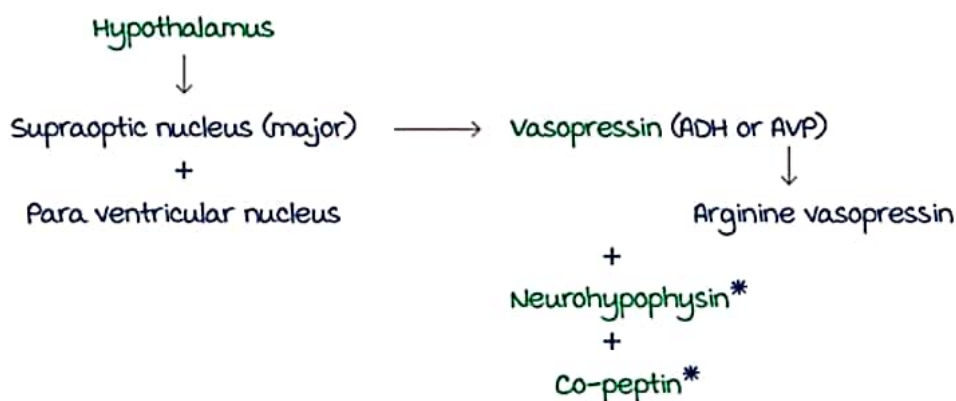


↑ in ACTH = ↑ in MSH → hyperpigmentation

- All the anterior pituitary hormones are regulated by hypothalamus
- Hypothalamus produces trophic hormone factors - TRH, CRH, GnRH, GHRH → trophic factors are secreted into hypothalamohypophyseal portal system via the pituitary stalk → reach anterior pituitary
- Prolactin inhibitory factor produced by hypothalamus regulates prolactin
- Prolactin is the only hormone that is under inhibitory control of the hypothalamus

Active space

- The pathway through which dopamine inhibits prolactin → tubuloinfundibular pathway
- Relationship between hypothalamus and anterior pituitary → hypophysiotrophic relationship



- ADH produced in the hypothalamus goes to the posterior pituitary → stored there via nerve fibers in the stalk
- The relationship between the posterior pituitary and hypothalamus → neurohypophysial relationship

Development of anterior pituitary

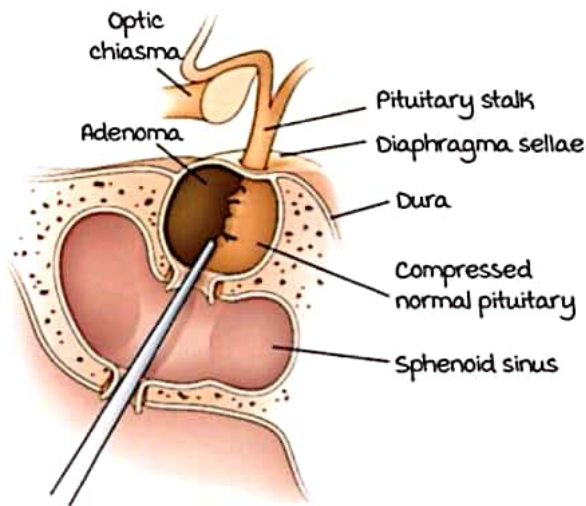
00:11:51

- Development of anterior pituitary is from Rathke's pouch → neuroectodermal derivative, actually a diverticulum or upgrowth
- Posterior pituitary develops as a down growth from the floor of the 3rd ventricle
- most common cause of congenital hypopituitarism → pituitary dysplasia
- In pituitary dysplasia, the hormones of posterior pituitary are intact
- Cells from the Rathke's pouch need to migrate across the midline to reach the anterior pituitary → in pituitary dysplasia midline craniofacial defects are present

Anatomy:

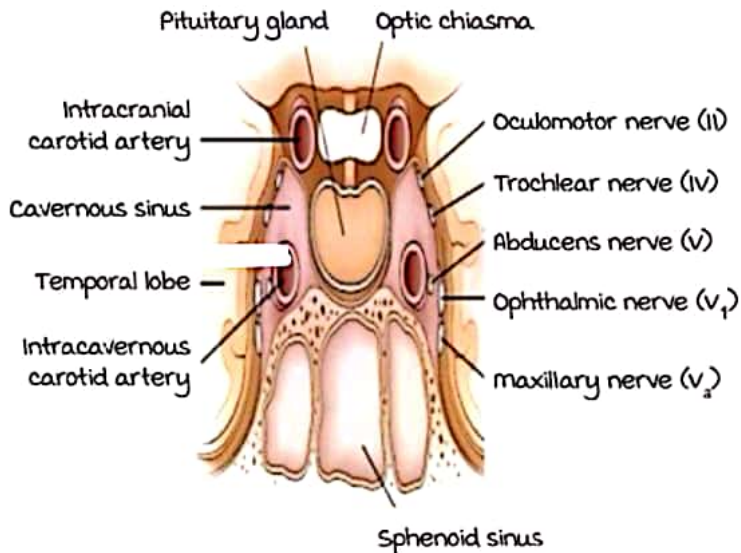
- The anterior pituitary is situated in a bony cage called sella turcica

Posterior relationship:



- Posterior relationship of anterior pituitary is sphenoid sinus
- Surgery → preferred approach is trans sphenoidal approach

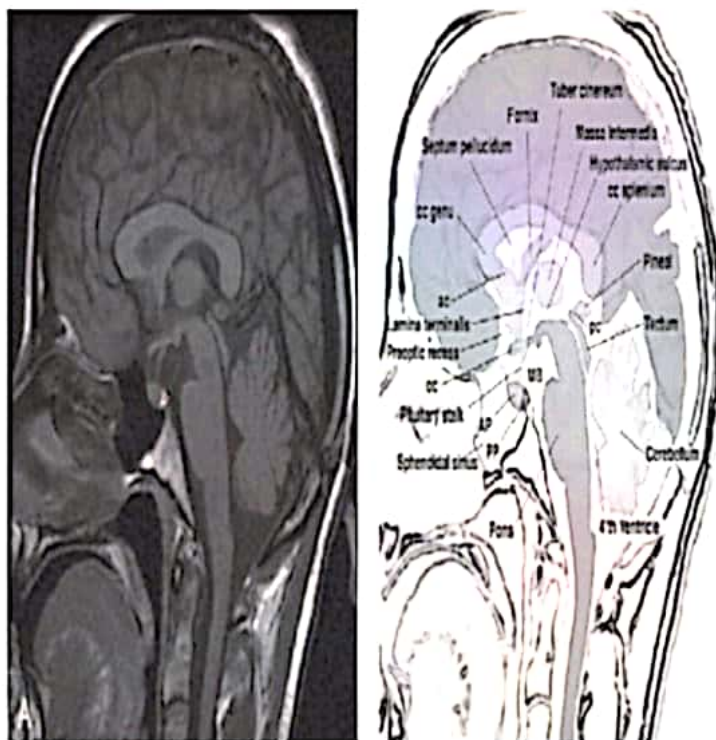
Lateral relationship:



- Pituitary tumour can expand to cavernous sinus/ lateral wall of cavernous sinus/ temporal lobe
- Inside cavernous sinus - 6th nerve & internal carotid artery
- On lateral wall of cavernous sinus - 3,4,5 (ophthalmic & maxillary branch)

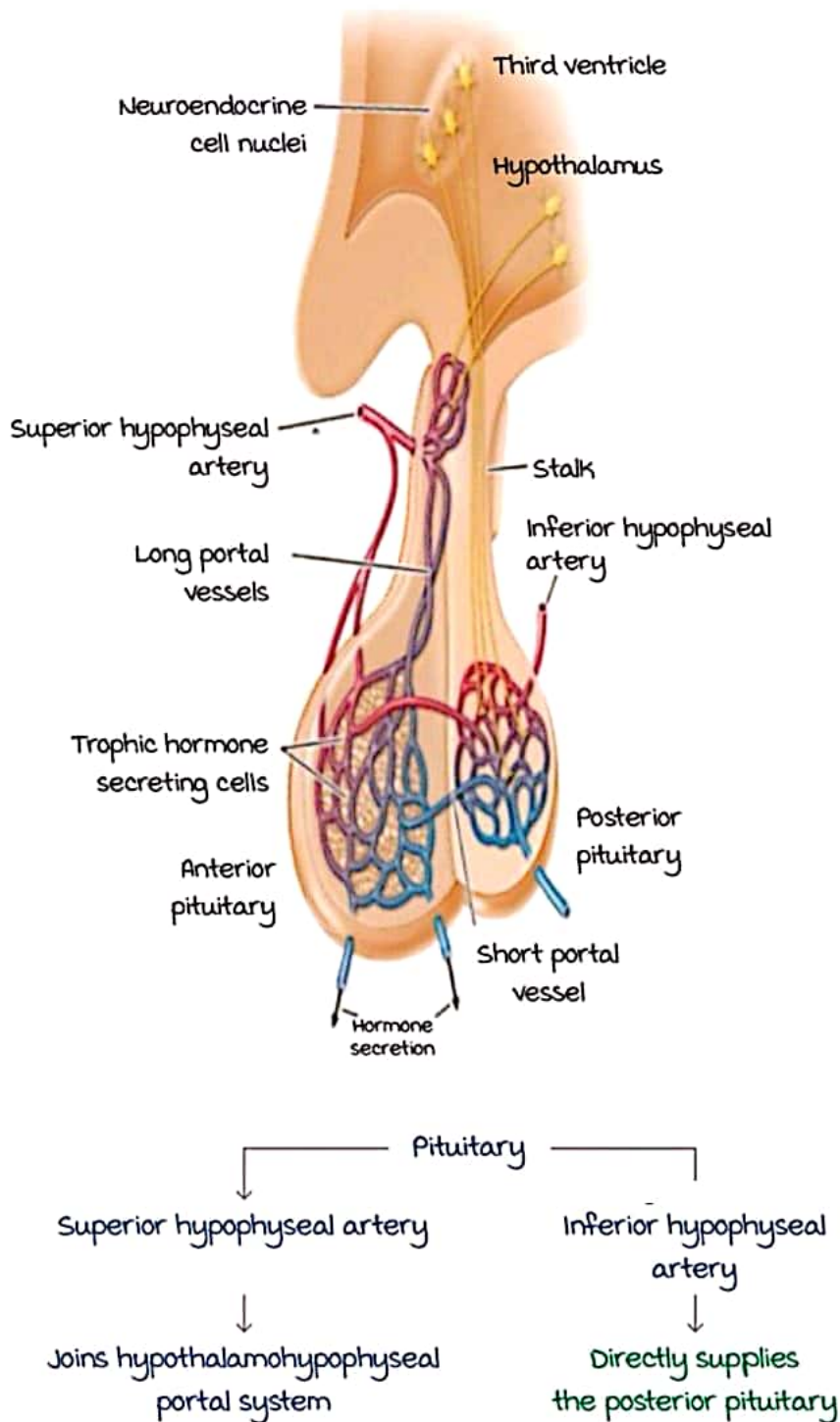
Anterior/ventral relationship :

- Ventrally covered by a layer of dura → called as Diaphragma sellae
- The line of least resistance for the tumor is ventral
- On T, sagittal image, the white spot (or) bright spot helps in the identification of posterior pituitary
- When a tumor enlarges, it first compresses the pituitary stalk before it compresses the optic chiasma to cause heteronymous or bitemporal hemianopia



- Effects of tumor
 1. Hormonal effect : Producing acromegaly, prolactinoma etc
 2. Stalk effect : Compression on the stalk, affects control of hypothalamus on the anterior pituitary hormones. So, hormones reduce.
Prolactin increases, this phenomenon of hypopituitarism + hyperprolactinemia is called stalk effect
 3. Mass effect : Compression + ICT symptoms

Blood supply of pituitary:



- metastasis to pituitary are carried by inferior hypophyseal artery
- mc malignancy to metastasise to pituitary : carcinoma breast
- mc manifestation of pituitary metastasis absence of ADH [central diabetes insipidus]
- The first cells to develop at 6 weeks are corticotrophs

- Transcription factors are required for the release of anterior pituitary hormones
- TSH, ACTH, GH, PROLACTIN - Pit -1 & PROP-1 are the transcription factors
- For FSH, LH - SF -1 & DAX 1
- % of total secretory cells in the anterior pituitary - 50% are growth hormone secreting cells
- GH cells > FSH, LH > ACTH & TSH
 - 1st - GH cells
 - 2nd - Prolactin producing cells
- In hypopituitarism, the first hormone to decrease is growth hormone

Table - Hormone secreting cells of the human anterior pituitary gland

Cell type	Hormones secreted	% of total secretory cells	Stain affinity	Diameter of secretory granules (nm)
	growth hormone	50	Acidophilic	300-400
Lactotrope	prolactin	10-30	Acidophilic	200
Corticotrope	ACTH	10	Basophilic	400-550
Thyrotrope	TSH	5	Basophilic	120-200
Gonadotrope	FSH, LH	20	Basophilic	250-400

- Next hormones to decrease are FSH & LH & ACTH
- Even in the absence of TSH, Thyroid can produce T_3 & T_4 ; hypothyroidism not a component of hypopituitarism
- GH & Prolactin producing cells - Acidophilic - twin hormones
- ACTH, TSH, FSH & LH producing cells - Basophilic
- Largest diameter of secretory granules - corticotrophs

Prolactin

00:37:22

- Produced by lactotrophs and acts via JAK STAT receptor (peptide hormone)

Function:

- It induces and maintains lactation in a breast already primed by estrogen
- Prolactin is also produced from placenta, uterus and other parts of CNS

Physiological inhibitor:

- Physiological inhibitor of prolactin is dopamine → pathway called tubuloinfundibular pathway

Physiological stimulators

- Estrogen
- TRH
- VIP
- Oxytocin

Hyper prolactinemia:

- Fasting prolactin levels – normal – $<25 \mu\text{g/L}$
- Physiological hyperprolactinemia – $25-40 \mu\text{g/L}$

Causes:

- Pregnancy & lactation
- REM sleep *
- Stress
- Chest wall stimulation

- Prolactin levels – $40 - 100 \mu\text{g/l}$ – a) Drugs b) Systemic disorders
- Prolactin levels – $>100 \mu\text{g/l}$ – Probably due to tumors
- Prolactin levels – $> 250 \mu\text{g/l}$ – Tumor
Tumor size corresponds to prolactin levels

Causes of prolactin levels between 40– 100 $\mu\text{g/l}$:**Drugs: a) D_2 blockers**

- Typical antipsychotics – blocks mesocortical, tubuloinfundibular & nigrostriatal pathways
mesocortical block – worsening of negative symptoms
Tubuloinfundibular block – $\uparrow$ prolactin
Nigrostriatal block – extrapyramidal S/E
- Atypical antipsychotics – Only Risperidone produces hyper prolactinemia

b) Antiemetics – metoclopramide –

cross BBB – hyperprolactinemia

Domperidone – doesn't cross BBB –

No hyperprolactinemia

- Hyperprolactinemia due to drugs – value normalises within 72 hours

c. TCA/ SSRI'S – Can cause hyperprolactinemia, mild effect on D_2

d. Opiates

e. Verapamil

f. H_2 blockers

g. α – methyldopa

- systemic disorders with 40 – 100 $\mu\text{g/l}$ of prolactin:

1. CKD

2. Chronic liver disease

3. PCOS

4. Hypothyroidism * – TRH levels $\uparrow$

TRH can physiologically increase the prolactin levels

PROLACTINOMA

Prolactinoma

00:00:06

- mc tumor of pituitary is prolactinoma
- α - Subunit of FSH secreting tumors are more common than Prolactinomas, but they're clinically insignificant
- There are 3 types of Prolactinomas:
 - a. 90% of the Prolactinomas have < 1 cm size - microadenomas - 20 : 1 (F : M)
 - b. 9% of the Prolactinomas have 1-4 cm size - microadenomas - 1 : 1 (F : M)
 - c. 1% of the Prolactinomas have > 4 cm size - giant prolactinomas - 1 : 1 (F : M)
- Prolactinomas generally occur at the age of 25- 45yrs, mostly in Females
- A Prolactinoma which is occurring at an age <20yrs is due to a Genetic Syndrome unless proven otherwise
- The 3 Genetic syndromes associated with Prolactinomas are
 1. MEN -1 syndrome
 2. McCune Albright syndrome
 3. Carney's complex
- A tumor occurring in a female (25-45 years) generally presents with hormonal effects rather than mass effect or stalk effect because 90% of them are microadenomas. In males, they are diagnosed late
- clinical presentation in 25-45 year old females:
 - 1) GALACTORRHEA AMENORRHOEA COMPLEX (mc)
 - 2) INFERTILITY FOR EVALUATION (luteal phase dysfunction)
- In males, the mc presentation - loss of libido, erectile dysfunction
- Prolactinomas can produce osteoporosis of spine
- Prolactinomas can also cause insulin resistance

Diagnosis of prolactinoma

00:08:42

Screening test of choice:

Fasting prolactin levels

- If $>100 \mu\text{g/L}$ - It can probably due to a tumor
- If $>250 \mu\text{g/L}$ - Its definitely a tumor

Hook effect:

The patient has got a tumor, but prolactin levels are normal

The patient will have symptoms

repeat the test in serial dilutions

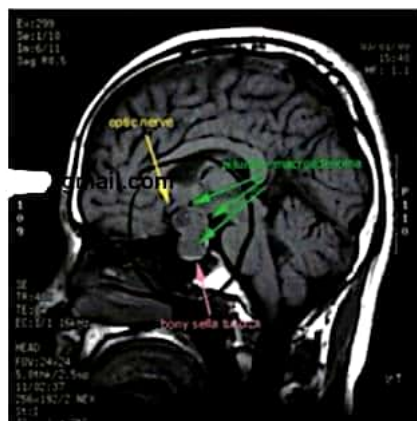
macroprolactin:

very high prolactin levels in the absence of tumor. Patient is asymptomatic. This is functionally insignificant macroprolactin. measure the levels of macroprolactin (macro) specifically

Confirmatory test:

Gadolinium enhanced MRI

- Prolactinomas do not take up contrast uniformly



T1w CEMRI coronal image showing a pituitary macroadenoma with bilateral parasellar, supra- and infrasellar extension with encasement of both carotid arteries in a 54-year-old male with hyperprolactinemia

Indications of treatment:

- All macroadenomas and symptomatic microadenomas must be treated
- Asymptomatic microadenomas are not treated.
- Repeat MRI after 6 - 8wks → increase in tumor size → treated

Treatment:

- Goal of the treatment is
 - a. Prolactin levels should be normalized
 - b. Tumor should shrink in size
 - c. Hypogonadism must be corrected.
- The First line of treatment of prolactinoma is always medical irrespective of the size of tumor

DOC:

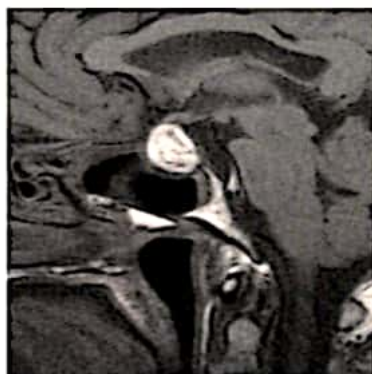
- Oral Dopaminergic agonists - Cabergoline > Bromocriptine
- Cabergoline has long $t_{1/2}$ So, given twice weekly - 0.25 mg
- S/E of cabergoline are less - Vomiting & postural hypotension are less compared to Bromocriptine.
- Bromocriptine is preferred in pregnancy

Follow up:

- medical treatment for 1 month → repeat prolactin levels, (usually gets normalized)
- Tumor shrinkage takes 3 months - 6 months
- Symptomatically patient gets better by 1 month
- If symptoms are not reduced or prolactin levels are still high, the Patient is considered as dopamine agonist resistant tumor after 1 month of treatment with drugs.
- Dopamine agonist resistance is seen in < 20% patients
- Generally Dopamine agonist resistant patients are also Dopamine agonist Intolerant .
- In dopamine agonist resistance
 &
 dopamine agonist intolerant } surgery
- If patient is improving on drugs, to be given for "2 years"
- Risk of malignancy in prolactinoma - < 0.01%
- marker of malignancy - Ki67
- Bromocriptine in pregnancy → stopped 7 days prior to lactation

Indications of surgery:

- a. Dopamine agonist resistance
 - b. Dopamine agonist intolerant
 - c. mass effects not improved after 1 month
 - d. Pregnancy, no response in 1 month
 - e. Bleeding into pituitary – **pituitary apoplexy** – white on T₁ image
- Surgery – Transsphenoidal resection.

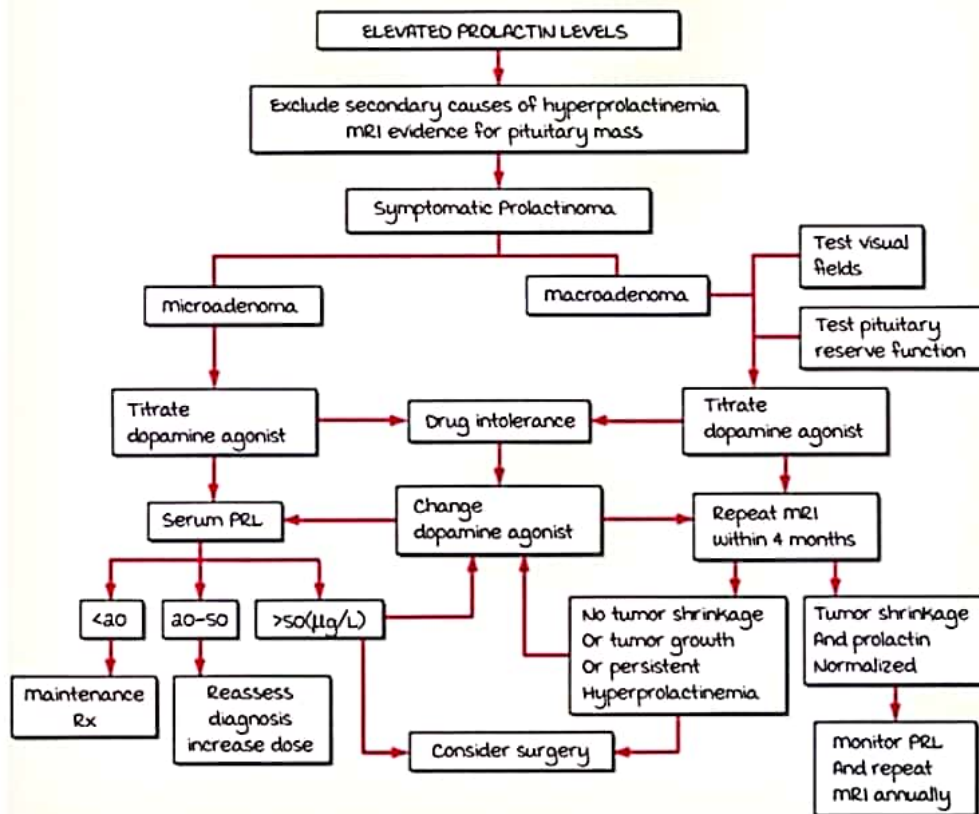
**Radiotherapy:**

- Only if patient is medically unfit for surgery



- T₁W image showing invasive giant prolactinoma in 28yr old lady (left)
- T₁W image of same patient after 9m of medical treatment showing complete disappearance of tumor (right)

MANAGEMENT OF PROLACTINOMA



ACROMEGALY

Pituitary adenoma

Prolactinoma > GH secreting adenomas > ACTH secreting adenoma
 most common (microadenoma) (macroadenoma) (macroadenoma)

FSH }
 LH } Secreting adenoma rare
 TSH }

Growth Hormone (GH)

00:02:15

- Produced by somatotrophs
- Constitutes >50% cells in anterior pituitary (Acidophilic)
- GH & Prolactin acts by JAK - STAT pathway



Twin hormones

- $t_{1/2}$: 5 - 20 min
- Pulsatile release

GH	vs	Prolactin
• Increase during stage 2 & 4 NREM sleep • Physiological stimuli 1) GHRH from hypothalamus 2) Ghrelin from stomach • Physiological inhibitor		• Increase during REM sleep • Physiological stimuli 1) Estrogen 2) TRH 3) VIP

Somatostatin

Stimulating factor GH for release

- Hypoglycemia
- Exercise
- Fasting

Inhibiting factor for GH release

- Aging
- Obesity
- Hypocaloric state / malnutrition



Causes GH resistance

Paradoxical GH release :

TRH given to a normal person → GH production will not increase

TRH given to a GH secreting adenoma pt → GH production doubles

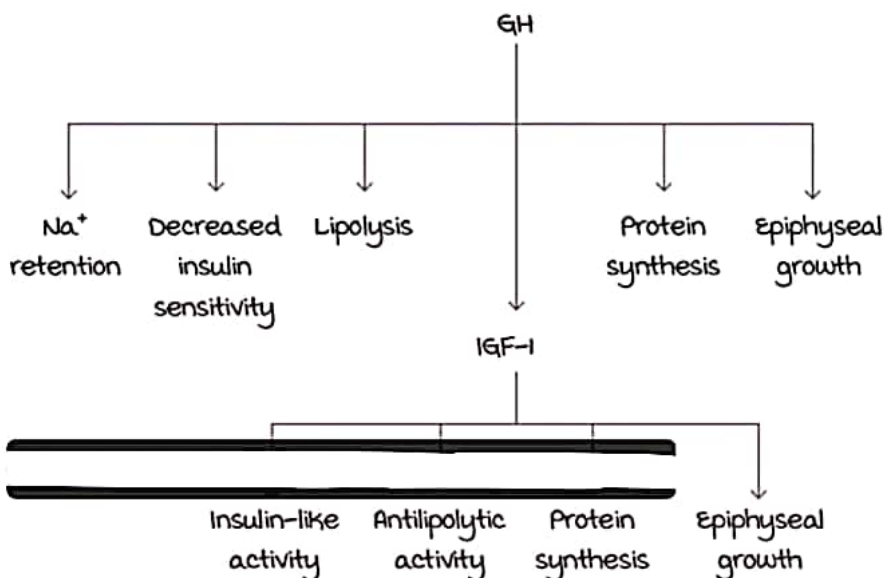


Paradoxical GH release

Peripheral actions of GH

00:09:24

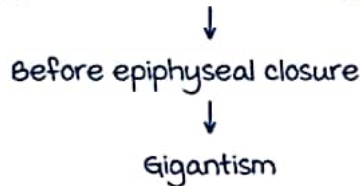
- Executed by IGF - 1
- Produced from the liver in response to GH binding to its receptors in liver
- IGF-1 also known as somatomedins C
- Structurally similar to insulin
- GH & IGF-1 has no effect on intrauterine height
- Intrauterine height depends on IGF-2 which is produced by diverse tissues



Acromegaly / GH secreting adenoma

00:18:37

- Growth hormone secreting tumor / adenoma
- Occurs after 40 yrs – after epiphyseal closure
- Only peripheral (acra) parts enlarge
- Results in acromegaly
- All the organs, soft tissue, cartilage enlarged
- If GH secreting adenoma occurs < 20 years age

Acromegaly

- Common in m > F
- Macroadenomas
- > 40 years
- If occurs in young pt < 20 years (genetic syndromes)
 - 1) MEN – 1
 - 2) Carney's complex
 - 3) McCune-Albright syndrome
- 98% of acromegaly are due to GH secreting adenoma
- Densely or sparsely granulated
- Of this, 20 % are somatomammotrophic adenoma (Prolactin + GH secreting)
- Remaining 2% causes
 - 1) Paraneoplastic GH secretion
Due to pancreatic islet cell tumor
 - 2) GHRH secreting tumor of hypothalamus
Due to Hypothalamic Hamartoma
 - 3) Paraneoplastic GHRH Release
Due to Bronchial carcinoid > small cell carcinoma lung
- Patient presents with
 - 1) Hormonal effect → GH excess
 - 2) Stalk effect
 - 3) Mass effect

Features of acromegaly

00:28:08

Coarse facial features

- 1) Prominent supra orbital ridges
- 2) Thick lips
- 3) **macroglossia**
- 4) Frontal bossing
- 5) Prognathism
- 6) Jaw malocclusion
- 7) **Deep husky voice**
- 8) Large hands and feet



Systemic changes:

I) Nerve, muscle

Entrapment neuropathies

myopathy - Due to atrophy of type II muscle fibres

II) Joints

- Arthritis involving large joints especially
- Due to synovial hypertrophy

III) Eyes

- **Angle closure glaucoma**

Cardiovascular system

- Hypertension
- Asymmetrical LVH $\xrightarrow{\text{Leads to}}$ Diastolic heart failure

Respiratory system

- ~~Soft tissue~~ proliferation
 - ↓
 - Obstructive sleep apnea**
 - ↓ leads to
 - Pulmonary hypertension**

Thyromegaly

- IGF - 1 acts on thyroid $\rightarrow$ Goitre

Colonic polyposis :

- Increased risk of malignancy compared to general population

Increased metabolic rate:

- Results in hyperhidrosis
- Seborrhoea

Increased salt & H_2O retention

- Due to $\uparrow$ Aldosterone levels
- One of the reasons for hypertension

Reproductive system

- Large tumor $\rightarrow$ Injury to stalk



Stalk effect



$\downarrow$ FSH, LH release



Hypogonadism

- Females with GH excess can have hirsutism

metabolic issues

- 1) Hyperglycemia $\rightarrow$ Insulin resistance
- 2) Hypertriglyceridemia / Hyperlipidemia
- 3) $\uparrow$ production of $1, 25 (OH)_2$ cholecalciferol



Excess Ca^{+2} & phosphorous absorption



Leads to **hypercalcemia, hyperphosphatemia**



Leads to hypercalcuria



Ca^{+2} oxalate stones

- Ectopic GH - Pancreas
- Pseudoacromegaly - conditions with acromegalic facies
 - Obesity
 - Hypothyroidism
 - Phenytoin therapy
 - IGF2 tumors
 - Insulinoma
- GH excess - Insulin resistance - Acanthosis nigricans

Increased metabolic rate:

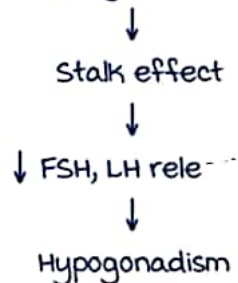
- Results in hyperhidrosis
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Increased salt & H_2O retention

- Due to $\uparrow$ Aldosterone levels
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Reproductive system

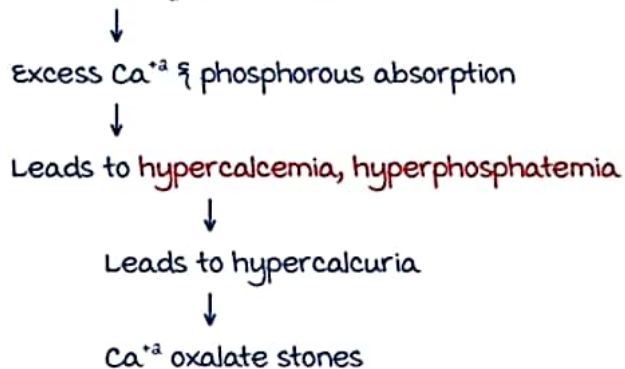
- Large tumor $\rightarrow$ Injury to stalk



- Females with GH excess can have hirsutism

metabolic issues

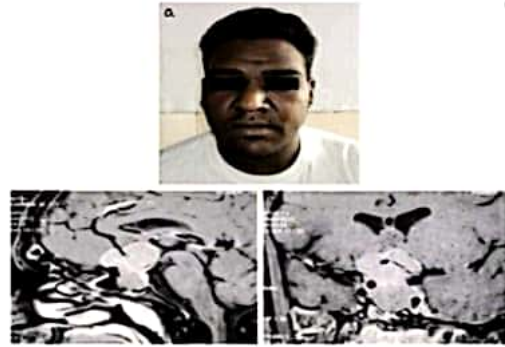
- 1) Hyperglycemia $\rightarrow$ Insulin resistance
- 2) Hypertriglyceridemia / Hyperlipidemia
- 3) $\uparrow$ production of $1,25(OH)_2$ cholecalciferol



- Ectopic GH - Pancreas
- Pseudoacromegaly - conditions with acromegalic facies
 - Obesity
 - Hypothyroidism
 - Phenytoin therapy
 - IGFA tumors
 - Insulinoma
- GH excess - Insulin resistance - Acanthosis nigricans

T₁ sagittal image post contrast

- Patchy uptake



T₁ coronal post contrast MRI

- Patchy uptake
- Hence it is macroadenoma, patchy uptake of contrast



GH secreting tumor



Acromegaly

Young female facial asymmetry



McCune Albright syndrome
due to presence of polyostotic
fibrous dysplasia



Diagnosis

00:48:07

1) Screening test:

- IGF-1 levels are measured
IGF-1 → Long t_{1/2}, non pulsatile release

2) Confirmatory test

- Oral glucose suppression test

75gm oral glucose



After 1 hr



GH levels < 1 ng/ml

Hyperglycemia



Suppress GH release



In normal person

If GH levels are $> 1 \text{ ng/ml}$ $\rightarrow$ Acromegaly

GH levels normally decreased due to

- 1) $\uparrow$ glucose
- 2) Somatostatin

If GH level $> 40 \text{ ng/ml}$ (very bad prognosis)

Investigation of choice:

Gadolinium enhanced MRI

Treatment

00:51:08

1) Always surgery - 1st line

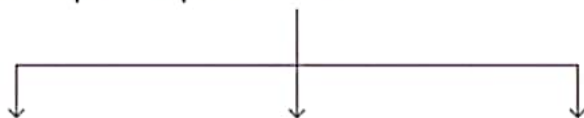


Transphenoidal surgical resection



Only 50% macroadenoma are cured

- microadenoma $\rightarrow$ 80% cure
- Relapse is common
- Immediate post-op GH estimation



GH detectable

- Risk of relapse is high



Drugs - 2nd line

GH not detectable

- Risk of relapse is low

1) Somatostatin analogues

- Lanreotide (drug of choice)

2) GH receptor antagonist

'Pegvisomant'

3) D₂ agonists

- Cabergolin
- Bromocriptine

Relapse cases:

- Go for 2nd surgery

Active space

- Patient medically unfit for surgery go for gamma knife stereotactic radiotherapy

Pituitary function tests:

- Done in all patients with acromegaly
- Because these are macroadenoma



Stalk effect



All the hormones are decreased except prolactin

NON-FUNCTIONAL PITUITARY MASSES

- Non endocrine tumors of pituitary
- These tumors causes stalk effect and mass effect

Stalk effect:

- Hypopituitarism → Because they are under positive control of hypothalamus
- Hyperprolactinoma → Because it's negatively regulated by Dopamine

mass effect:

- Due to compression
- Due to increased intracranial tension

Bleeding in to tumor → Known as **pituitary apoplexy**

clinical presentation :

- Headache
- Apoplexy
- Visual symptoms
- cavernous sinus thrombosis
- Hypopituitarism / Hyperprolactinemia

Non functional pituitary masses:

- 1) Craniopharyngioma
- 2) Rathke's cyst

Craniopharyngioma

00:04:00

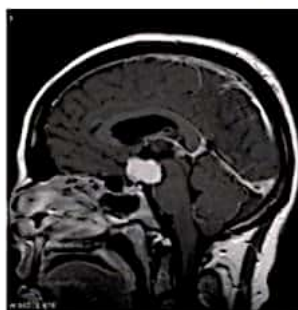
- most common non-functional pituitary tumor
- Bimodal age distribution : 5-15 yrs and 50-74 yrs
- 90% occurs in childhood

Craniopharyngioma

	Childhood	Adults
	90%---suprasellar + sellar	10%---suprasellar
	m > F	m = F
	Adamantinomatous	Papillary
	Cystic with machinery oil appearance >>>> solid	Solid
	Wet Keratin nodules	
	Calcification ++	-----
	Hyperintense on T ₁ with vivid enhancement	Hypointense

MRI Findings:

- T₁ sagittal precontrast
macroadenoma can be functional, non functional
- Functional Tumors → Hypointense on T₁
- Non - Functional Tumors → Hypo & hyperintense on T₁
- T₁ sagittal Post-contrast MRI
- vivid uptake of contrast → craniopharyngioma



Clinical features:

- Child of 5-15 yrs
- Presents with stalk effect followed by mass effect
- GH deficiency

- FSH/LH deficiency
- ACTH deficiency
- ADH deficiency
- Increased prolactin

Investigation of choice:

- Gadolinium enhanced MRI

Treatment:

- No medical treatment
- Transphenoidal surgery

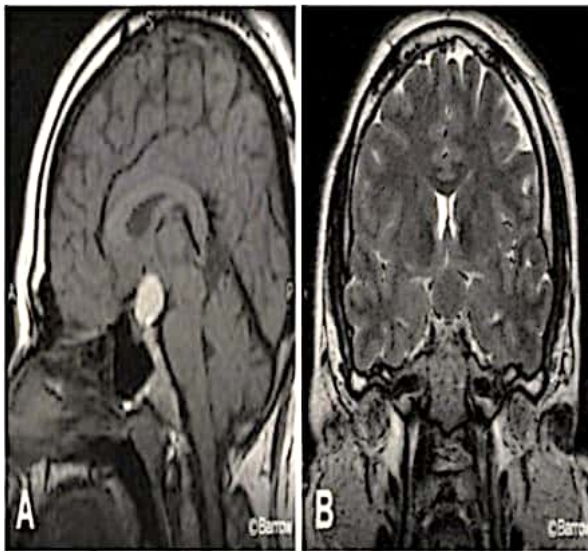
- T₁ sagittal precontrast image of Normal Pituitary

1) Anterior pituitary



Slightly hypointense

2) Bright spot



A-T₁ MRI image

- Slightly hypo to hyperintense lesion

B-T₂ MRI image

- Completely hypotense

Suggestive of Craniopharyngioma

Rathkes cyst

00:18:18

- Headache and visual disturbance
- presents as Stalk effect.

Rathke's cyst

- 1) 4th to 5th decade
- 2) site: Rathke's cleft
- 3) unilocular
- 4) well circumscribed
- 5) Sellar mass
- 6) No calcification
- 7) Lined by simple columnar epithelium

v/s craniopharyngioma

mostly in children

Infundibulum

multilocular

may & may not circumscribed

Suprasellar + sellar mass

Calcification present

Adamantinomatous and Papillary

MRI of rathkes cyst:

- 1) T₁ sagittal Pre contrast image
 - Hypointense lesion



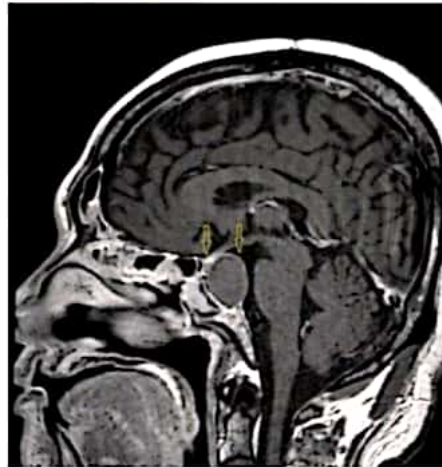
a) T₂ sagittal Post contrast image

- Only margins are takes up the contrast
- Characteristic of Rathke's cyst
- This sign is called 'Claw sign'
- Nodule inside the cyst



Dot sign

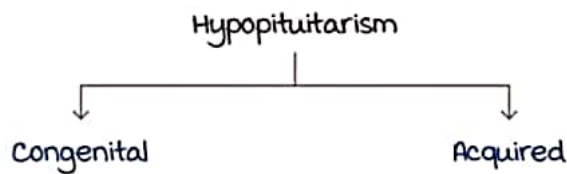
- Posterior ledge sign



case presentation:

1. Large lobulated suprasellar mass within 3rd ventricle causing obstructive hydrocephalus- **Germinoma**
2. Calcification / bony hyperstosis / Pneumosinus dilatans- **Meningioma**
3. Notochordal remnant with clivus destruction- **Chordoma**
4. Ring enhancing lesion- **Pituitary abscess (mcc)**
5. Claw sign / posterior ledge sign / dot sign- **Rathkes cyst**

CONGENITAL HYPOPITUITARISM

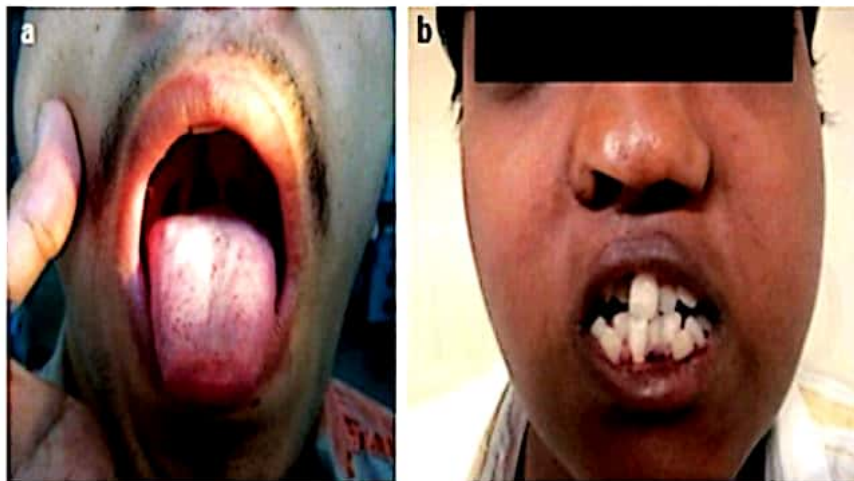


Congenital hypopituitarism

00: 01: 24

Causes:

- 1) Pituitary dysplasia which is always associated with **midline cranio-facial Anomaly**



midline defects in patients with hypopituitarism,

(a) bifid uvula,

(b) single central incisor

- 2) Transcription factor defect

Prop 1 > Pit - 1

- most often posterior pituitary will be intact
- Because Anterior pituitary development is different from posterior pituitary

3) Syndromes associated with congenital hypopituitarism

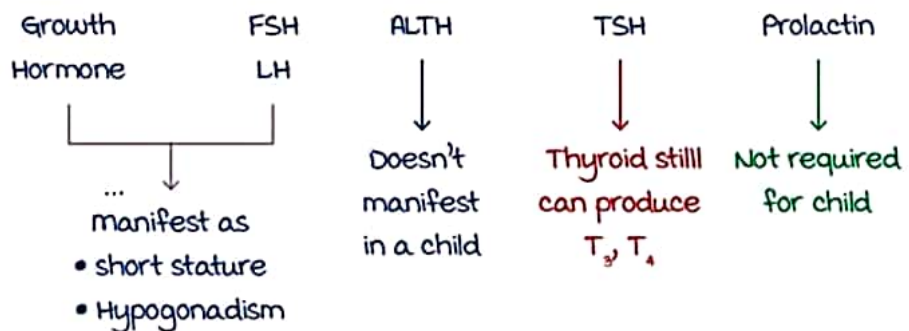
- Kallmann syndrome
- Laurence moon Biedl Bardet syndrome
- Septo-optic dysplasia
- Prader - willi syndrome
- Angelman syndrome

4) Other Genetic cause

- Leptin Receptor mutation

Deficiency of anterior pituitary hormones

00:04:28



So, child presents with

- Growth Hormone deficiency
- Hypogonadism (Hypogonadotropic hypogonadism)

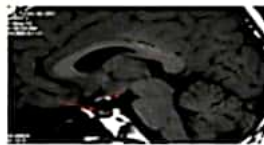
↓
FSH, LH - Low
↓
Sex Hormones - Low

Growth hormone deficiency

00:06:13

- Normal I.Q at every point in time
- Normal height at Birth (In utero → It depends on IGF-2)
- Child present with hypoglycemia ± seizures
- Prolonged physiological jaundice
- microphallus

- As the child grows → Centripetal obesity
Short stature
Delayed sexual development
Delayed dentition
High pitched voice even after puberty
- Short neck
- Proportionate short stature
- Growth velocity low since birth



micro phallaria
delayed puberty
short stature

- Round face with
- Frontal Bossing
- Depressed nasal bridge
- midline defects – cleft lip / palate / single central incisor / bifid epiglottis



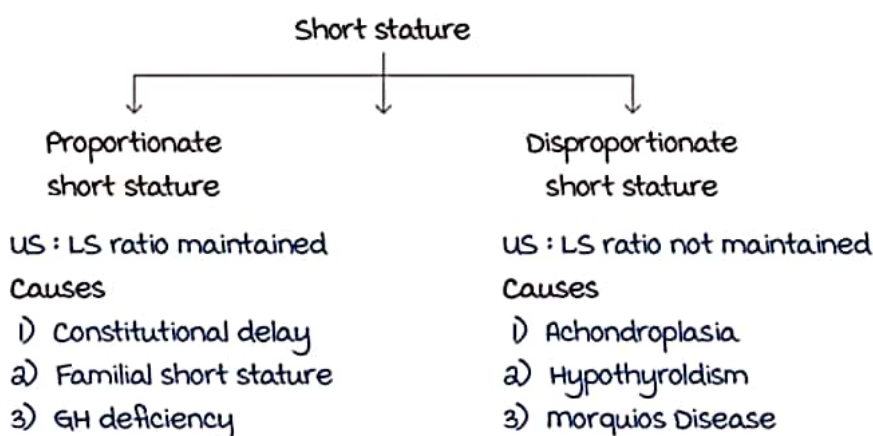
Short stature

00:11:07

- Height for Age is low by >2 standard deviation
- Or Height for Age $<92\%$
 - Height for Age
 - $>95\%$ - Normal
 - 90 - 95 % - Grade I stunting
 - 85 - 90% - Grade II stunting
 - 80 - 85% - Grade III stunting
 - $< 80\%$ - Dwarf
- Eg:- 10 yr old child, height = 124 cm
 - Expected height of 10yr old child = $6 \times \text{Age} + 77$

$$= 6 \times 10 + 77$$

$$= 137 \text{ cm}$$
- So, he is $<92\% \Rightarrow$ He is a short stature

**Proportionate short stature**

00:14:39

Constitutional short stature:

- Normal height at birth, height at 1 yr age also normal
- Normal height in Parents
- At 1-3 yr Age $\rightarrow$ Stops growing
- After 3 yr $\rightarrow$ Grows normally
- Delayed puberty by 2 yrs
- Eventually height becomes normal

$$\text{Height Age (HA)} = \text{Bone Age (BA)} < \text{Chronological Age (CA)}$$

Familial short stature

- Low height at birth
- Parents also have short stature

$$HA \ll BA = CA$$

GH deficiency:

$$HA < BA < CA$$

Treatment:

- Replacing GH – recombinant GH
- Dose: 0.18–0.35 mg/kg/week, S.C route
- >12 cm/yr → Expected gain in height
- Side effects of GH:

Hypertension

Gynecomastia

↑ risk of leukemia

Laron dwarfism

00:20:47

- GH Receptor mutation in liver
- Basal GH levels are high
- IGF – 1 levels very low
- IGF – 1 Binding proteins are very low
- Severe short stature
- Treatment – recombinant IGF



IPLEX (recombinant IGF + IGF Binding Protein)

Hypogonadism

In a child it manifests as

- Decreased body hair
- Eunuchoid Body Proportions (Armspan > height)
- Small prostate
- Scrotum smooth without rugosity
- Testicular volume < 6 cm³
- Penile length < 5 cm
- Testicular length < 2.5 cm

Post pubertal onset hypogonadism does not affect:

- 1) prostate size
- 2) penile length
- 3) scrotum
- 4) skeletal proportions

Syndromes associated with congenital hypopituitarism

00:26:09

Septo-optic dysplasia

- HESX1 mutation
- Degeneration of septum pellucidum
- Hypopituitarism + optic atrophy

Kallman syndrome

- X-linked recessive
- **KAL gene** on X-chromosome
- Agenesis of olfactory bulb → Anosmia
- Degeneration of GnRH producing neurons in Hypothalamus

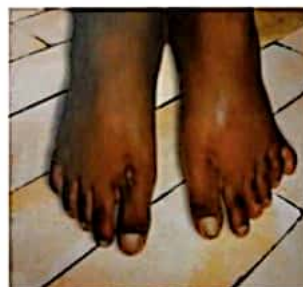


Hypogonadotropic hypogonadism

- It's associated with 3C's - optic atrophy (very rare)
 - Cleft palate
 - Cerebellar ataxia
 - Color blindness

Laurence moon biedl bardet syndrome

- Autosomal Recessive condition
- Hexadactyly or Polydactyly
- Obesity
- Hypogonadotropic Hypogonadism
- Severe mental Retardation
- Horse-shoe Kidney
- Retinitis Pigmentosa



Prader willie syndrome vs Angelman syndrome

- | | |
|---|---|
| <ul style="list-style-type: none"> • Genomic imprinting • maternal genes are imprinted (inactivated / silenced) • Paternal gene deletion • Or uniparental maternal disomy | <ul style="list-style-type: none"> • Genomic imprinting • Paternal genes are imprinted (inactivated / silenced) • maternal gene deletion • Or uniparental paternal disomy |
|---|---|

Features common in both Prader willie and Angelman

- Severe mental retardation
- Severe short stature
- Severe obesity
- Early onset diabetes
- Hypogonadism
- Acromicria (small hands)



Specific to angelman syndrome

- Severe muscle hypotonia
- Emotional issues → Inappropriate Laughter



Happy puppet syndrome

ADULT HYPOPITUITARISM

Acquired hypopituitarism

00:00:14

Causes :

- I Stalk effect [mc cause of Acquired hypopituitarism]
 1. Pituitary macroadenomas [Functional or Nonfunctional]
 2. Infiltrative
 1. Sarcoidosis
 2. Hemochromatosis
 3. Langerhan cell histiocytosis
 4. Autoimmune
 - Lymphocytic hypophysitis
 3. Infections
 1. TB
 2. Pneumocystis carinii pneumoniae
 3. Histoplasmosis
 4. Toxoplasmosis
 4. Traumatic resection of stalk
- II Pituitary infarction or necrosis
 1. Postpartum pituitary necrosis → Sheehan syndrome
 2. Russel viper venom bite .
- III Secondary Empty Sella Syndrome [Tumor or bleed]

Hormones involved

00:05:20

GH FSH/LH ACTH ADH TSH } Prolactin }	acquired hypopituitarism
Due to " stalk effect " It shows involvement of Anterior and posterior pituitary	

- Due to "pituitary dysplasia"
- development of Anterior and posterior pituitary is different.
- So, posterior pituitary is not affected

Congenital hypopituitarism

Order of Hormones :

GH > FSH / LH > ACTH

Isolated hormone deficiencies may be seen in any order

In emergencies [Bleeding or Apoplexy] → "ACTH"

Adult GH deficiency

00:06:52

1. Impaired quality of life energy or self esteem concentration
↓
2. Body composition [Decrease in lean body mass - centripetal obesity]
3. Reduced Exercise capacity
4. Cardiac Issues
 1. Atherosclerosis
 2. Hyperlipidemia

Adult FSH/LM deficiency

00:09:10

- Hypogonadism

male → Decreased libido
Defective ejaculation / erection
Sexual drive ↓ ↓
Decreased body hair
"Osteoporosis" ++

In-post pubertal

onset → Scrotum [Normal]
Penile length [Normal]
Skeletal proportions [Normal]
Prostate [Normal]

Female

Amenorrhoea / Oligomenorrhoea
Infertility
Hot flushes

In Clinical presentation wise : Female hypergonadism > male hypergonadism

ACTH Deficiency

00:11:24

↓ Cortisol

Fatigue / asthenia / tiredness

Loss of appetite

Loss of weight

Unexplained Hypoglycemia

unexplained Hypotension

but to military cause.

Central Diabetes Insipidus

Polyuria

Pituitary Function Test

00:12:53

TSH ; FSH ; LH ; Prolactin $\longrightarrow$ Can be estimated directly

Two hormones cannot be estimated directly

- GH
- ACTH

GH :

GH provocative Tests [$< 3 \text{ ng/dl}$]

In this Test, we administer, 1. GHRH

2. Arginine

After giving these, GH level is expected to increase above

3ng/dL : if not, it is considered as GH deficiency

[L - dopa ; clonidine ; Glucagon are used but not approved]

ACTH :

1. Insulin tolerance Test
2. metyrapone Test
3. ACTH stimulation Test [cortisol deficiency]

It is not a pituitary function test, used to assess adrenal reserve

Insulin Tolerance Test [Not done ; risky Test]

0.1 unit / kg of Regular Insulin I.v eg : 50kg $\rightarrow$ 5 units.

After 0 ; 30 ; 60 ; 90 min etc. look for cortisol level

Done after recording fasting cortisol [should be Normal]
 When insulin is administered to a Normal person $\rightarrow$ Hypoglycemia $\rightarrow$
 Increase in cortisol level [$> 20 \text{ Ng/dl}$]

If it is $> 20 \text{ ug/dL}$ $\rightarrow$ low ACTH reserve

Interpretation of the Test :

1. ACTH low or Cortisol low $\longrightarrow$ Test +ve
2. metyrapone Test [Steroid Synthesis Inhibitor]
 on giving metyrapone $\longrightarrow$ Deoxycortisol is not converted to
 Cortisol $\longrightarrow$ So, In normal person
 ACTH level will be increased .

If ACTH levels fail to increase then it is considered as positive Test .
 This implies ACTH is poor .

metyrapone test is better than insulin tolerance test ; because Insulin
 tolerance test is positive in both adrenal and pituitary

Sheehans Syndrome

00:19:46

- postpartum pituitary necrosis
- $> 75\%$ necrosis required for its manifestation .
- Anterior pituitary doubles in size during pregnancy
- In post partum Hemorrhage
 In 1/10,000 deliveries,
 Low pressure portal System is unable to $\uparrow \uparrow$ se
 blood supply $\rightarrow$ Abrupt onset of hypotension $\rightarrow$
 hypoperfusion $\rightarrow$ Infarction or Necrosis .

Progression of hormone loss :

GH $>$ FSH ; LH $>$ ACTH $>$ TSH



LH $>$ FSH

[posterior lobe is spared]

Clinical Features :

fatigue
 Failure to resume periods
 Failure of lactation
 +
 Hypothyroidism

GH
 FSH; LH; ACTH; PRL; TSH } ⇒ Decreased
 ADH → mostly Normal

Sheehan syndrome complications :

1. Adrenal crisis → Hypotension
2. Severe hyponatremia
3. Severe osteoporosis
4. Weight loss

Important differential diagnosis Lymphocytic Hypophysitis

Lymphocytic hypophysitis

00:25:26

Autoimmune inflammation of Pituitary only seen in "post partum period" present as Inflammatory mass in the pituitary

mass is made up IgG containing lymphocytes and plasma cells .

mostly seen in females having Autoimmune Illness .

Naturally have stalk effect + mass effect

Any post partum female presenting with a pituitary mass has to be given a trial of steroids .

Sheehan	Lymphocytic hypophysitis
pituitary necrosis No mass Hormonal profile: GH, FSH ; LH ; TSH ; ACTH ; prolactin all are low ADH → Normal	mass ++ Stalk effect Hormonal profile : GH ; FSH ; LH ; ACTH ; TSH all are low Prolactin → ↑ ↑ ADH → low mass takes up contrast in Imaging study Macroadenoma in Acromegaly will take patchy uptakes of contrast .

Features of lymphocytic hypophysitis

1. pituitary enlargement.
2. headache , visual disturbances
3. hypopituitarism
4. hyperprolactinemia
5. associated autoimmune disease.

Empty sella syndrome

00:31:26

Empty Sella Syndrome → Sella is Empty

Primary empty Sella : Does not produce Hypopituitarism

Secondary empty Sella : Produce Hypopituitarism

cause - Tumors

- Post bleeding

Primary empty sella syndrome

00:32:28

↑^{se} ICT → CSF sweeping down into pituitary

Because Rim of pituitary is intact patient generally does not develop hypopituitarism

↑^{se} ICT → Benign intracranial hypertension
or
pseudo tumor cerebri.

Pituitary apoplexy

00:35:14

Acute Intra pituitary Hemorrhage .

In patients with post partum necrosis

or
tumor
or

Spontaneously [Hypertension or DM or sickle cell
Anaemia]

present with History of 1-2 days Headache / vomiting ± meningeal
irritation

Clinical presentation -Acute

Hypoglycemia / Hypotension / worsening headache

In bleeding → Hormone most affected is ACTH

In pituitary apoplexy → Bleeding ++ So, All hormone are "low."

Treatment :

IV Steroids + urgent surgical decompression

Treatment of hypopituitarism

00:38:54

Steroids

Due to sort durattion of action - Oral Hydrocortisone

If vomiting or hypotension - I.V hydrocortisone

If there is stress / infection - Double the dose

Based on circadian Rhythm

10mg	5mg	5mg
[8-9 am]	[1-2 pm]	[4-5 pm]

Conversion dose :

1 mg Dexamethasone = 4 mg methyl Prednisolone = 5 mg prednisolone
= 20 mg Hydrocortisone = 25 mg cortisone

L-Troxine 50mg /day → 200mg /day

L-troxine can worsen Hypocortisolemia.

so L-Troxine given after steroids.

FSH/LH replacement

00:42:15

In males :

Testosterone gel or patch or I.M Testosterone enanthate

200mg once in every 2 weeks

Desiring fertility → GnRH

In females : [who completed their family]

Estrogen 1mg Day 1 → 25

Progesterone 5mg Day 16 → 25

For Fertility → Gonadotrophins or Ovulation induction agents.

Gh therapy in adults

GH → 1 mg s/c once daily (or)

oral GH - 0.3 mg /day

ADH

ADH → Intranasal desmopressin 5-10 mg BD

or

Oral desmopressin 0.3-0.6 mg once daily

Genetic syndrome involving pituitary

00:45:51

Patient with prolactinoma or Acromegaly [in young patient]

Consider three syndromes in young patients with prolactinoma or acromegaly

1. MEN -1 syndrome

Prolactinoma > GH secreting tumor

2. McCune Albright Syndrome

GS α mutation

features

a) cafe au lait spots

b) precocious puberty

c) Polyostotic fibrous dysplasia with facial asymmetry

d) pituitary adenoma [GH > Prolactin]

3. Carneys Complex / Syndrome

PPKAR - 1a gene

a) Lentigenes [Spotty skin lesions]

b) Adrenal cushing [Lean cushings]

c) Atrial myxoma

d) Pituitary [GH > Prolactin]

Carney's triad → GIST + Pulmonary

Chondroma + Paraganglioma

Nelson syndrome

00:48:37

ACTH secreting macroadenoma

Rapid progression due to loss of negative feedback

Extreme hyperpigmentation

Symptoms due to Expanding Intracellular mass lesion

Transsphenoidal surgery

Sheehan and its complications :

Wrinkling → due to GH deficiency

Dryface / expressionless → due to hypothyroidism

First Hormone to be lost → GH

Second Hormone → TSH

COMPLICATIONS :

- Adrenal Crisis → Hypotension
- Severe Hyponatremia
- Severe osteoporosis
- Weight loss
- Pituitary apoplexy

POSTERIOR PITUITARY

Posterior pituitary [neurohypophyseal relation]

00:00:30

Hormones → Hypothalamus

↓ Via stalk

Stored in the

Posterior pituitary

Released when required

- Vasopression

- Oxytocin

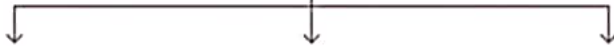
Posterior pituitary → [down growth from the floor of 3rd ventricle]

ADH / Vasopressin or Arginine Vasopressin (AVP)

00:01:40

Produced from **Supraoptic nucleus or paraventricular nucleus of Hypothalamus**

Preproarginine vasopressin



Neurohypophysin a

Copeptin

ADH

Receptors :

$V_1(V_1a)$

V_a

$V_3(V_1b)$

$V_1(V_1a)$:

Blood vessels → **Vasoconstriction**

Platelets → **Aggregation**

Liver → **Glycogenolysis**

uterus → **Contraction**

myocardium → **Hypertrophy**

$V_3(V_1b)$:

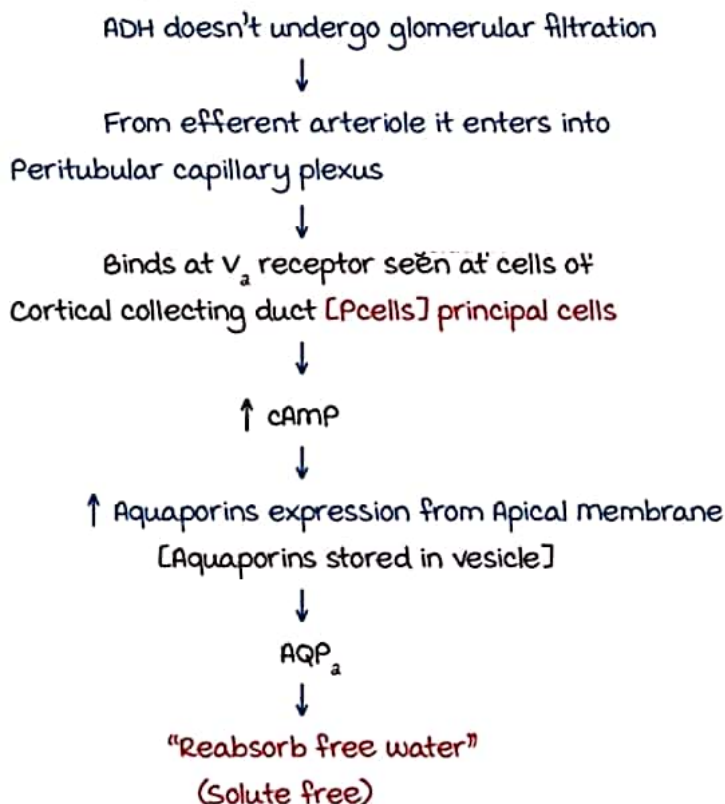
Anterior pituitary → **↑ ACTH release**

Active space

V_a :

Vascular endothelium → Release VWF → Platelet adhesion
Kidney

Function of ADH:



Two types of water reabsorption

00:09:19

Obligatory water reabsorption	Facultative H_2O Reabsorption
- Independent of ADH - Acts at proximal convoluted tubule - Aquaporins involved: AQP_1 AQP_7	- Dependent on ADH - Acts at collecting duct - Aquaporins involved: AQP_a

Aquaporins

00:10:42

1. AQP ₁ ; AQP ₇	PCT
2. AQP ₂	Apical membrane
3. AQP ₃ ; AQP ₄	[B/L] Basolateral membrane of collecting duct
4. AQP ₆	Inside vessels of collecting duct
5. AQP ₅	No Role in kidney

Glomerular filtrate

Normal: Serum osmolality 285-290 mosm/kg of H₂O

Osmolarity of the filtrate remains same after reabsorption in PCT [sr. osm - 285-290] This phenomenon is called "Iso osmotic reabsorption"



At tip of loop of Henle (Sr.osm-1200mosm)

H₂O is reabsorbed in the thin descending limb to reach maximum filtrate osm -1200 mosm

This process is called "Counter current multiplication"



Lowest filtrate Osmolality [50 mosm] At DCT

[∴ Through Thick Ascending limb → Solutes are reabsorbed]

From 50 mosm to 800-900 mosm/kg



Concentration gradient ↑ by using ADH

Factors required for ADH to function :

1. medullary Interstitial Osmolality
2. Urea
3. Vasorecta



Counter current exchange

Defence mechanism to prevent hyponatremia

00:18:55

Both Hypo and hypernatremia are the disorders of water metabolism

$$\text{Serum osmolality} = 2 \times \text{Na} + \frac{\text{Blood glucose}}{18} + \frac{\text{BUN}}{2.8}$$

$$= 285 - 290 \text{ mosm/kg of H}_2\text{O}$$

Low osmolality = Low Na

Low osmolality = Hyponatremia = "True Hyponatremia"

If Na^+ low but Osmolality Normal or High

= Pseudo - Hyponatremia

High Na^+ is never equal to High osmolality :

Osmolality is Normal < 285-290 mosm/kg

$\therefore$ ADH levels are kept below 1 ng/l

> 280 - 285 mosm/kg

ADH $\uparrow\uparrow$



Free H_2O reabsorption



Osmolality Normal

> 290 mosm/kg

supra optic
osmoregulatory centre



$\uparrow$ Thirst



free H_2O reabsorption
osmolality Normal

High Na^+ = High Osmolality :

In Neurosurgery cases : Patient with head injury or on ventilator,

Pituitary apoplexy $\rightarrow$ ADH not released $\rightarrow$
hypernatremia, otherwise hypernatremia
is rare

Adipsic hypernatremia

00:28:48

Disease of Hypothalamus $\rightarrow$ Damage to osmoregulatory
Centres of supraoptic nucleus

Low Osm = Low Na^+

High Osm $\neq$ High Na^+

Normally ADH is $< 1 \text{ ng/l}$, when osmolality $\uparrow\uparrow$ = ADH release $\uparrow\uparrow$ = Brings Osmolality to Normal

If, ADH is released with a low osmolality:

SIADH (Syndrome of Inappropriate ADH)

Low Na^+ = Hyponatremia

SIADH

00:34:20

I Head Injury

II Paraneoplastic

- SCC lung
- Caudodenum
- Capancreas
- Thymoma

III Drugs

- Chlorpropamide
- Clofibrate
- Cyclophosphamide
- Carbamazepine
- Chlorpromazine
- TCA / SSRI
- Vincristine
- Oxytocin; Nicotine

IV Acute necrotizing pneumonias

V Acute meningoencephalitis

VI Acute Intermittent porphyria

Criteria

00:37:17

1. Low serum Osmolality
2. Urine Osmolality $>$ Serum Osmolality
3. Clinically euvolemic
4. Urinary Na^+ $> 20 \text{ meq/L}$
5. Absence of pituitary, adrenal, thyroid, renal and liver disease

If free H_2O reabsorption more $\rightarrow$ Tendency for $\uparrow$ intravascular volume $\rightarrow$ RAS(-) inhibited $\rightarrow$ Aldosterone $\downarrow\downarrow$ urinary Na^+ $\uparrow\uparrow$
 $\rightarrow$ Atrial Natriuretic factor $\uparrow\uparrow \rightarrow$ So, urinary $Na^+ = > 20 \text{ meq/L}$

Diabetes Insipidus [DI]

00:39:51

No ADH $\rightarrow$ Central DI

Resistance to ADH $\rightarrow$ Peripheral or Nephrogenic DI to ADH

Polyuria: [$>50 \text{ ml/kg/24hrs}$ or 3.5 L/.24hrs]

Solute diuresis

1. Tubular injury
2. mannitol
3. Urine dipstick **+ve** for glucose

Water diuresis

1. $> 7 \text{ L}$
2. Urine dipstick $\rightarrow$ “-ve”
3. Urine osm $< 500 \text{ mosm}$
4. Urine specific gravity ≤ 1.010

Causes for water diuresis

00:44:28

1. Central DI
 2. Nephrogenic DI
 3. Psychogenic polydipsia
- $\Rightarrow$ To differentiate water deprivation test

Water deprivation test

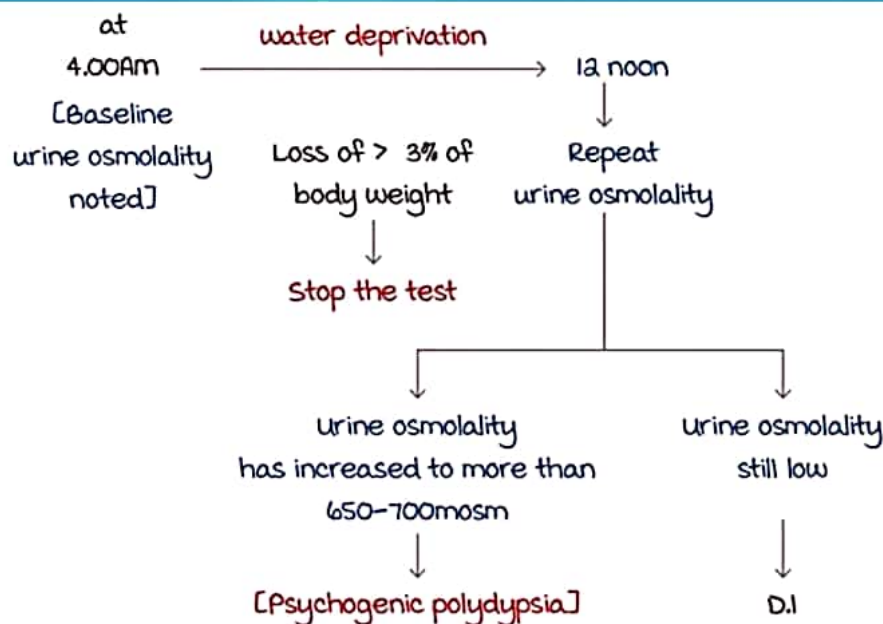
00:45:26

Urine Osmolality

Central DI $< 250 \text{ mosm}$

Nephrogenic DI $250-450 \text{ mosm}$

Psychogenic DI $450-600 \text{ mosm}$



- [If urine osmolality still low after 12noon give Intranasal desmopressin on S/C aqueous vasopressin and check at 2pm and 4pm for urine osmolality]

At 4 pm

If urine osm ↑ by > 50% → Central D.I
[in 4hrs] [12-4pm]

If urine osm ↑ by < 10% → Nephrogenic D.I
[in 4hrs]

If urine osm ↑ by 10 - 50 % → Partial central D.I
[in 4hrs]

Central D.I

00:50:44

Acquired	Genetic [AR]
1 Stalk effect	DIDMOAD syndrome [WOLFRAM]
- Pituitary adenoma [MCC]	Diabetes insipidus
[Functional/Non - functional]	DM
- Infiltrative	Optic atrophy
[Sarcoidosis; LCH; Autoimmune; Hemochromatosis]	Deafness
- Infection [TB; PCP; Toxoplasmosis, Histoplasmosis]	
- Traumatic	

Active space

II Pituitary infarction [eg: Sheehan; ADH deficiency rare]

III Pregnancy [Vasopressinase]

major symptoms:

Polyuria

The patient able to drink water



No hypernatremia

Nephrogenic DI [peripheral]

00:54:38

I Drugs

Lithium

Demeclocycline

Cisplatin

Aminoglycoside

Foscarnet

Amphotericin B

II Chronic tubulo interstitial disease [ADH resistance]

Causes:

- 2 Autoimmune disease [Sjogren; Sarcoidosis]

- 4 metabolic

↑ Ca

↓ K

↑ Uric Acid

Hyper oxaluria

- childhood kidney disease

Reflux Nephropathy

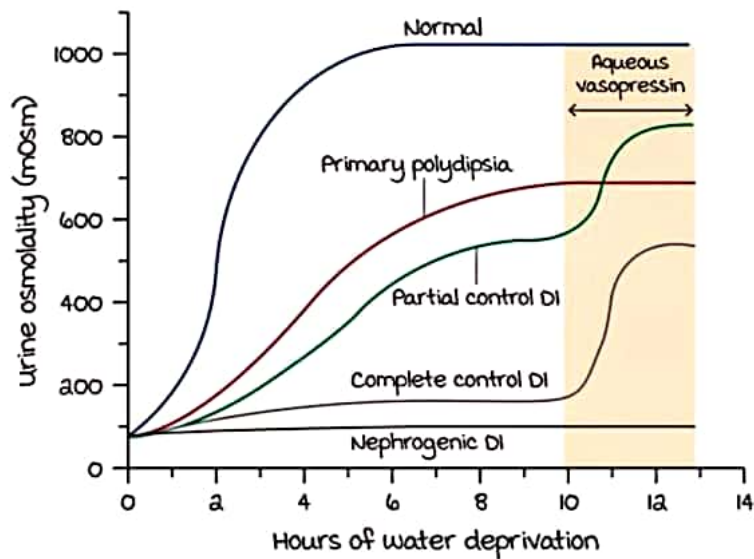
III Pregnancy

IV Sickle cell Anaemia

Genetic causes

- V_a Receptor mutation [XLR] more common
- AQP_a mutation [AR]

Water deprivation test: Interpretation



Treatment

1:00:06

Central D.I :

Intranasal desmopressin 10-20g bd

Partial D.I :

Aqueous S/C vasopressin

Or

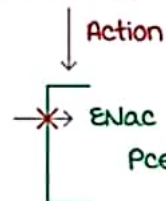
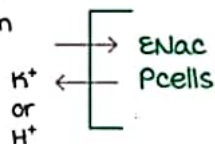
Clofibrate

Or

Carbamazepine

Peripheral D.I :

Lithium Induced D.I → Amiloride or Triamterene

Lithium
Action

Other drug used for peripheral D.I → Thiazide diuretics

Action : volume contraction

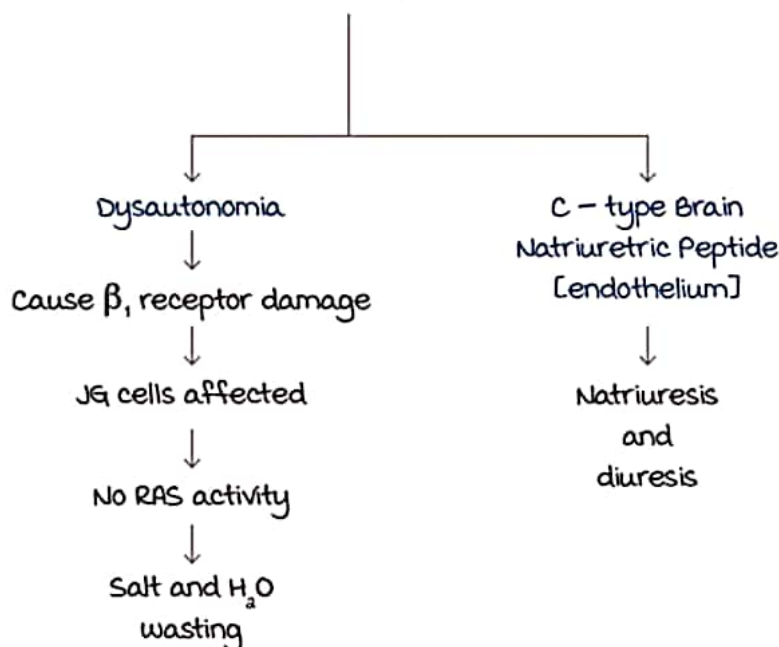
↑ responsiveness of other parts of tubule

2 Causes for Hyponatremia post – head injury

1. SIADH

2. Cerebral salt wasting syndrome [CSWS]

(CSWS) Cerebral Salt Wasting Syndrome



Present as Dehydration

Hypovolemia

Hypovolemic Hyponatremia

Occurs in 1-2 weeks after Head injury resolves in
3 - 4 weeks

Normal uric acid levels

CSWS	SIADH
1. Polyuria	No polyuria
2. Hypovolemic hyponatremia	Euvolemic hyponatremia
3. Dehydration	No dehydration
4. Present after 1-2 weeks of head injury	Presents immediately after head injury
5. Treatment: Fluids [Hydration]	> 48 hrs water restriction
6. normal uric acid levels	Decreased uric acid levels

WATER METABOLISM

Hyponatremia and Hypernatremia

00:00:21

Hyponatremia [Disorders of H_2O metabolism]

According to European care of Intensive care unit

Serum $Na^+ < 120-125$ meq/L are associated with symptoms

∴ [There is no strict normal value for Na^+ differs from person to person]

115-120/125 meq/L → GI symptoms

Anorexia

Nausea / Vomiting

Cramps

$<110/115$ meq/L → mild neurological

Agitation

Confusion

Dizziness

Ataxia

↓ concentration

$<100-105$ meq/L → Serious neurological symptoms Cerebral edema

↑ ICT

[Cerebral edema → in hyponatremia- blood osmolality is low - water diffuses from high to low concentration (from capillaries into interstitium)]

STEP 1: True vs Pseudo Hyponatremia

Low osmolality

High osmolality or Normal osmolality

eg- serum Na - 92, BUN- 28, blood glucose- 90

$$\text{Serum Osmolality} = 2 \times Na + \frac{\text{Blood glucose}}{18} + \frac{BUN}{2.8}$$

$$= 2 \times 92 + \frac{90}{18} + \frac{28}{2.8}$$

$$= 184 + 5 + 10$$

$$= 199 \text{ mosm/kg/H}_2\text{O}$$

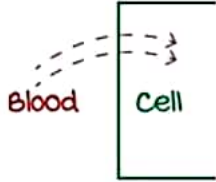
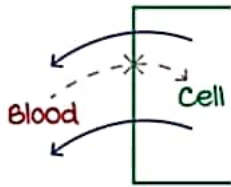
$$= \text{True Hyponatremia}$$

Active space

Pseudo hyponatremia

Low Na^+ ; Osmolarity $\uparrow$ or $\uparrow$ sed

a) Translocational Pseudo Hyponatremia

 Certain solutes that easily cross from blood to cell membrane "Ineffective solute" Eg: Alcohol	 Certain solutes that cannot easily cross from blood to cell membrane remain in blood compartment; So, this $\uparrow$ se osmolality of blood compartment; water from cell diffuses to blood: So, more water in blood results - Hyponatremia. These solutes are "effective solutes" 1. Glucose 2. mannitol 3. Glycine 4. maltose Eg: Polyuria [in DM]
---	---

b) methodology

Flame spectro photometry to measure Na^+ [old] $\uparrow$ se proteins $\uparrow$ se lipids $\downarrow \text{Na}^+$ This is also considered as "pseudo hyponatremia"	Ion sensitive electrodes [New] This is not seen here
--	--

Causes for pseudohyponatremia:

1. Glucose
2. mannitol
3. Glycine
4. maltose

→ By Translocation

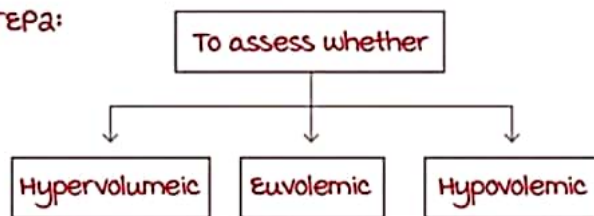
5. ↑ proteins
6. ↑ lipids

→ By old methodology

Step 2: Evaluation of hyponatremia

00:11:45

STEP2:



Hypovolemic Hyponatremia

- CKD
- Cirrhosis
- Congestive Heart failure
- Nephrotic syndrome

Pathogenesis -

Aldosterone ← RAS ← Depleted Intra vascular volume

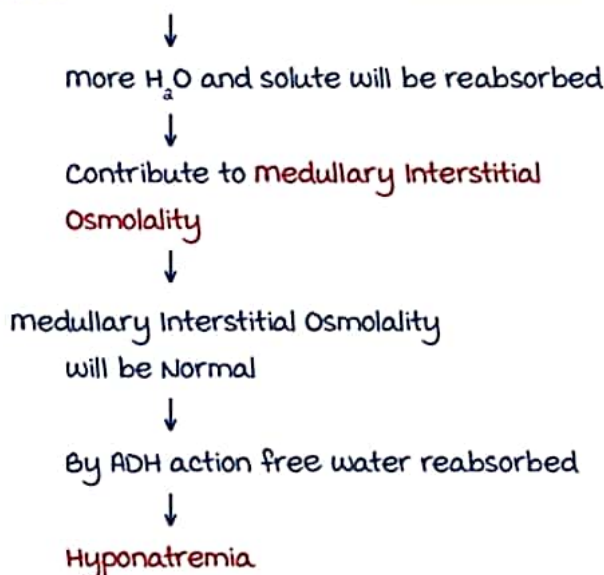
↓
absorb Na^+ and H_2O [$\text{Na}^+ < \text{H}_2\text{O}$]
⇓

Hyponatremia

Treatment: "Loop Diuretics"

Drug induced hyponatremia – thiazide or furosemide 00:14:35

Thiazide >> furosemide Thiazide: ↑ responsiveness of other parts of tubules



Furosemide:

Potent diuretic

Excrete salt and water

It excretes more water than sodium

Hypovolemic hyponatremia

00:17:30

Non renal loss	Renal
1. Vomiting 2. Diarrhea 3. 3 rd space loss → Burns → Pancreatitis → Rhabdomyolysis	1. Overuse of diuretics 2. Acute tubular injury 3. Renal tubular acidosis 4. Aldosterone insufficiency

Cerebral salt wasting syndrome → Also cause Hypovolemic Hyponatremia

Euvoletic hyponatremia

00:19:35

1. Cortisol insufficiency
2. Hypothyroidism
3. SIADH

Criteria – SIADH

00:20:08

Five criteria:

1. ↓ serum osmolality
2. urine osmolality > serum osmolality
3. Clinical euvolemia
4. ↑ urine Na^+
5. Absence of pituitary, Adrenal, Renal
6. Thyroid; Liver disease

Common cause SIADH → Head injury
manifest with → Hyponatremia

Treatment

00:21:20

Hypovolemic Hyponatremia:

Fluids are the mainstay

$$1\text{L of a fluid} = \frac{\text{Infusate Na} - \text{Sr.Na}}{\text{T.B.W} + 1 \text{ (Total body water)}}$$

$$\begin{aligned} 1\text{L of NS } 154 \text{ meq of Na} &= \frac{154 - 100}{60\% \times \text{BW} + 1 \text{ (Body weight 60 kg)}} \\ &= \frac{154 - 100}{36 + 1} = \frac{54}{37} \\ &\quad (60\% \text{ of BW}) \end{aligned}$$

1 L Normal saline will increase sodium by 1-2 meq/L [max:
1.5 meq/L]

Target correction ⇒ max - 8 meq/L / day

5 litres of Normal saline per day required

Treatment of acute SIADH

00:23:55

Acute symptomatic Hyponatremia

[within 48 hrs] It is considered as emergency to ↑ se Na+ Fluid of choice: Hypertonic saline or 3% saline

$$1 \text{ L} = 513 \text{ meq of Na}^+$$

$$100 \text{ ml} = 51.3 \text{ meq of Na}^+$$

Treatment option - 1

100 ml if 3% saline over 10 min repeated thrice

$$= \frac{\text{Infuse Na}^+ - \text{Sr. Na (95)}}{\text{TBW} + 1}$$

$$= \frac{513 - 95}{37}$$

$$= \frac{418}{37}$$

$$= 12 \text{ meq/L [11-12 meq/L]}$$

$$1 \text{ L [3\% NS]} = 11 \text{ meq/L}$$

$$500 \text{ ml} = 5.5 \text{ meq/L}$$

$$250 \text{ ml} = 2.75 \text{ meq/L}$$

$$[3-4 \text{ meq/L}]$$

Treatment option - 2: "Round the clock"

If we want to correct 8 meq/L

Ex:

$$= \frac{513 - 95}{37} = [11-12 \text{ meq/L}]$$

$$1 \text{ L [3\% NS]} = 11 \text{ meq/L}$$

$$\frac{1}{11} \times 8 = \frac{8}{11} = 700 \text{ ml}$$

So, 700 ml [3% NS] (100 mL) → 24Hrs

7 Bottles over 24 Hrs

1 Bottle over every 3.25 hrs

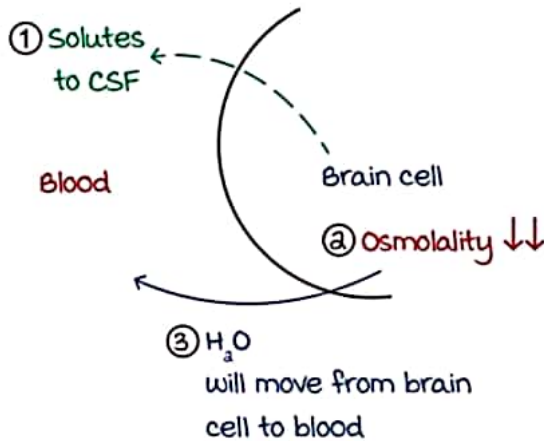
Treatment option 1 >> Treatment option 2

Central pontine myelinolysis

00:31:13

If $\uparrow$ ICT symptoms present

Same management

After 48 hrs $\rightarrow$ Brain compensates

④. Brain will shrink in size to assume optimum position

⑤. After 48 hrs 3% saline if given - blood osmolality further $\uparrow$, more H_2O diffuses from Brain cell to Blood and it causes further shrinkage in Brain

If Na^+ corrected $> 8\text{meq/L}$ in 24 hrs or using 3% NS

after 48 hrs without symptoms,

causes

osmotic demyelination $\rightarrow$ Central pontine myelinolysis

Central pontine myelinolysis manifest like a pseudobulbar palsy - B/L Hypertonia; B/L Hyper reflexia; Rigidity $\uparrow$ Tone

Sr. Na^+ Correct upto $[120 \text{ meq/L}]$



Water restriction → Treatment of choice

Salts

Urea

DOC: Vaptans [V_2 Antagonist]

Demeclocycline [$(-)$ cAMP]

Vaptans

00:37:36

1. Non selective [$\text{V}_1 + \text{V}_2$]

2. Selective [V_2]

Non-Selective: Conivaptan I.V or oral

Vaptans → No Role in Acute condition

In chronic Asymptomatic or mild symptomatic



use, selective vaptans [V_2]: Tolvaptan (5 mg) [oral]

Tolvaptan → major side effect → Hepatotoxicity

Is contraindicated in Hypovolemia

Can be used in Hypervolemia

Classification

Class of receptor block	Name
unselective (mixed V_1/V_2)	Conivaptan
V_1 selective (V_1RA)	Relcovaptan
V_2 selective (V_2RA)	Nelivaptan
V_2 selective (V_2RA)	Lixivaptan mozavaptan Satavaptan Tolvaptan

Hypernatremia

00:40:37

Hypernatremia – 'State of water deprivation' or water deficit

Preferred fluids: $\frac{1}{2}$ NS;

5% dextrose;

Free H_2O max correction of Sr. Na $\rightarrow$ 8meq/L

$$\text{Water deficit} = 0.6 \times BW \times \left[\frac{Na - 140}{140} \right]$$

$$\text{eg- sr. Na} = 160, BW = 60 = 0.6 \times 60 \times \left[\frac{160 - 140}{140} \right]$$

$$= 36 \times \frac{20}{140}$$

$$= \frac{36}{7} = 5 L$$

Half normal saline infusate $Na^+ = 77 \text{ meq}$

$$1 L \text{ of Half normal saline} = \frac{77 - 160}{37}$$

$$= \frac{83}{37} = 2 \text{ meq/L}$$

$$\begin{aligned} 1 L \text{ of } \frac{1}{2} NS &\rightarrow \uparrow Na^+ \text{ by } 2 \text{ meq/L} \\ 4 L \text{ of } \frac{1}{2} NS &\rightarrow \uparrow Na^+ \text{ by } 8 \text{ meq/L} \end{aligned}$$

Here, water deficit = 5L

with $\frac{1}{2}$ NS correct upto 4L

Remaining will be corrected in otherway [free water by 1L] Ryle's Tube

5% Dextrose $\rightarrow$ No Infusate Na^+

$$1L \text{ of } 5\% \text{ dextrose} = 4 \text{ meq/L} = \frac{0 - 160}{37}$$

$$2L \text{ of } 5\% \text{ dextrose} = 8 \text{ meq/L}$$

4L of $\frac{1}{2}$ NS $\gg$ 2L of 5% dextrose

ADRENAL MEDULLA – BASICS, PHEOCHROMOCYTOMA

- Adrenal medulla → 20% of adrenal gland
- Neural crest cell (neuroectodermal) derivative
- medulla develops before cortex - 45 days of gestation
- Synthesize 3 major hormones (peptide hormones) from tyrosine

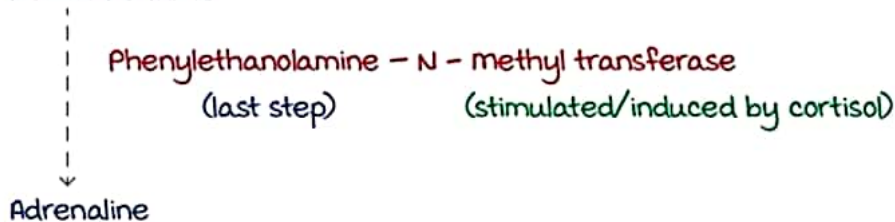
Adrenaline (epinephrine) (80%)	Nor adrenaline (nor epinephrine) (15-18%)	>> Dopamine (2%)
--------------------------------------	---	------------------

- Large dense granules → Noradrenaline
- Small dense granules → Adrenaline
- Opioids & chromogranin A are produced from the granules
- Adrenomedullin is produced from vascular endothelium (not adrenal medulla) in response to free radical injury

2 Functions:

- 1) Vasodilation
- 2) ? free radical scavenger

- Nor-adrenaline



Pheochromocytoma

00:06:44

- Catecholamine secreting neural crest cells tumor arising from
 1. Adrenal gland - Adrenal pheochromocytoma
 2. Sympathetic / Parasympathetic ganglia - Extraadrenal pheochromocytoma / paraganglioma
- 'Rule of 10' is outdated and no longer used

Active space

- Adrenal pheochromocytoma (75%) (adrenaline > Noradrenaline)
rarely dopamine
- Extra adrenal pheochromocytoma (25%) (exclusively Noradrenaline)
 - Sympathetic ganglia (20%)
 - Parasympathetic ganglia (5%)
- Sympathetic ganglia → Paraganglioma develops in abdomen or mediastinum
(mc site - organ of zuckerkanal)
- Parasympathetic ganglia → Carotid body > jugular bulb

Sporadic v/s familial

- 60% sporadic: 40% familial (mostly bilateral)
- Familial are associated with
 - 1) MEN-2
 - 2) VHL
 - 3) NF-1
- Sporadic presents in 40-50 yrs of age (m = F)
- Familial presents in 20-25 yrs of age (m = F)

Clinical presentation

00:06:44

- mc presentation → Panic attacks (75%)
(but <1% with panic attack have pheochromocytoma)
- 25% presents as Incidentaloma (25%)
- Classical triad →
 - 1) Episodic headache
(mc symptom - 90 to 95%)
 - 2) Profuse sweating
 - 3) Tachycardia
- Can present as episodic HTN (60%) > sustained HTN (20%)
- Can also presents with orthostatic hypotension
 ↑ Catecholamines → Deplete intravascular volume
- "6PW" of pheochromocytoma
 - 1) Pain
 - 2) Pallor
 - 3) panic attack
 - 4) Palpitation
 - 5) Profuse sweating
 - 6) Postural hypotension
 - 7) weight loss

- Weight loss, volume depletion and hyperglycemia in pheochromocytoma is due to **increased sympathetic drive**
- Normally, in pheochromocytoma, there is **↑ erythropoietin - polycythemia** (if there is pallor, suggestive of **malignancy**)
- Abdominal pain in pheochromocytoma is due to **hypercalcemia**
- Hypercalcemic can also leads to,
 - 1) **Polyuria (nephrogenic DI)**
 - 2) **Stones**
- Surest sign of malignancy → **metastasis**
- malignancy → Extraadrenal > adrenal
- **Succinate dehydrogenase B (SDH B) mutation** is associated with malignancy

When to suspect?

00:25:53

- According to endocrine society of india (ESI)
 - 1) **Hyperadrenergic spells**
 - 2) **Resistant young hypotension**
 - 3) **MEN -2 / VHL / NF-1**
 - 4) **Incidental adrenal mass**
 - 5) **Family h/o pheochromocytoma**
- mc sign → **Episodic hypertension**

Pathology

- Neural crest cell markers →
 - 1) **Chromogranin**
 - 2) **Synaptophysin**
 - 3) **S 100**
- **Zellballen pattern appearance ⊕**
- Organ maximally affected → **Heart (pheocardiomyopathy)**
Due to pheocrisis / HTN crisis
- In heart →
 - 1) **↑ HR**
 - 2) **↑ excitability**
 - 3) **↑ O₂ consumption**
 - 4) **↑ force of contraction**
- **↓ plasma volume; Hypercalcemia**

- Carbohydrate metabolism → Diabetic state
 - 75% of patients would have experienced postural hypotension at some point of time
 - Sympathetic paraganglioma is more functional than parasympathetic
 - Familial syndromes are bilateral except neurofibromatosis
 - Catecholamines are released in a pulsatile manner, there is no point in measuring blood or urine catecholamines levels
- ↓
- metabolites of catecholamines
(fractional metanephrines) is measured

Screening test

00:32:28

- Patient presents with panic attacks
- ↓
- 24 hours urine fractionated metanephrine (98% sensitivity, 98% specificity) → Negative
- ↓
- Still having features suggestive of genetic syndrome or family history
- (100% sensitivity) Plasma fractionated metanephrines ←
- 24 hours urine fractionated metanephrine
- ↓
- Positive → IOC (Gallium 68 - Dotatate scan)
(octreotide scan)
- MRI abdomen is done first then only Gallium 68 - Dotatate scan
 - For extraadrenal pheo, directly do Gallium 68 - Dotatate scan
 - MIBG scan is not used anymore

Treatment

00:38:28

- I. Sporadic pheo → Laparoscopic retroperitoneal Adrenalectomy (u/L)
- II. Genetic pheo → B/L partial adrenalectomy

Preparation for surgery:

- 1) Admit 7-10 days prior to surgery
 - 2) Volume repletion
 - 3) 7 days prior to surgery → Non-selective, irreversible, long acting α -blocker (phenoxybenzamine) → 10 mg OD
 - 1) Phentolamine
 - 2) Prazosin also used
 - 4) 3 days prior to surgery → β -blockers (Propranolol 50mg Q6H then once daily)
 - 5) Nifedipine, metyrosine - can also be tried
- Patient develops hypertensive crisis → DOC (sodium nitroprusside)
 - Next line →
 - 1) Nifedipine
 - 2) Phentolamine
 - Clonidine suppression test (0.3 mg clonidine is given)
 - Clonidine - presynaptic α_2 agonist - normally blocks catecholamines
 - In pheochromocytoma, release is not blocked
 - Drugs interfering with metanephrine assay;
 - 1) TCA
 - 2) L-dopa
 - Drugs precipitating HTN crisis
 - 1) β -blockers alone
 - 2) Glucagon
 - Post op follow up with 24 hr urine fractionated metanephrines

ADRENAL MEDULLA: MEN, MEON, PGA SYNDROME

Multiple endocrine neoplasia (MEN)

00:00:22

MEN-1 (Wermer syndrome) [AD]:

- Due to mutation in **MENIN gene** (Chromosome 11q)
- MENIN gene is tumor suppressor gene (TSG)
- mc mutation → **Inframe deletion** (frame shift mutation)

major manifestations

1. Parathyroid

- Every single patient by 40 yrs in MEN-1 have parathyroid involvement
- usually seen by 20-25 yrs
- mc & earliest manifestation of MEN - 1
- B/L parathyroid gland hyperplasia



Primary hyperparathyroidism (100%)

Sporadic 1°

I. > 60 yrs

II. F >> M

MEN-1 RELATED 1°

< 40 yrs

F = M

← **Hypercalcemia** →

III. Adenoma >> Hyperplasia

Hyperplasia >> Adenoma

IV. **Asymptomatic hypercalcemia**

Aggressive hypercalcemia

1) Recurrent abdominal pain
due to stones/UTI

2) Acute abdomen

3) Neuropsychiatric
symptoms

→ **Sestamibi scan** is used to visualize PTH gland

→ Treatment → **Near total parathyroidectomy**

II. Pancreas:

- Pancreas involvement in 30 to 50% of patients with MEN-1
- MC → **Neuroendocrine tumor of pancreas**
 - 1) Non-functional P Poma (pancreatic polypeptide secreting tumor)
 - 2) Gastrinoma
 - 3) Insulinoma
 - 4) Glucagonoma
 - 5) VIPoma

Sporadic gastrinoma	MEN-1 gastrinoma
>40 yrs	20-40 yrs
Large	Small
Unifocal	Multifocal
Passaro's triangle	Duodenal wall
50-70% malignant	Less malignant (<10%)
Treatment - high dose PPI + surgery	

- In MEN I associated gastrinoma lymph node enlargement is present
- Gastrinoma are highly responsive to large dose PPI (60-80mg)
- Surgery is not required for gastrinoma except in **pancreatic tumor with size > 2cm** (MEN - I related gastrinoma)
- For sporadic gastrinoma → Surgery done
- Insulinoma
 - I. Sporadic → >40 yrs (**Head > body > tail**) (90% benign)
 - II. MEN - I → <40 yrs (**Head = body = tail**) (50% benign)

III. Pituitary

- 15 to 20% of patient with MEN-1
- **Prolactinoma > GH secreting adenoma > ACTH Secreting adenoma**
- In prolactinoma < 20 yrs in MEN-1, 20-45 yrs in sporadic

Minor manifestations

00:15:12

- I) Adrenal adenoma/ pheochromocytoma / cortical tumor
 - mostly benign

2) Primitive Neuro endocrine tumor

- Thymic carcinoid
- Foregut carcinoid
- **Bronchial carcinoid**

3) Cutaneous

- **Angiofibroma** > collagenoma > lipoma

4) CNS tumors

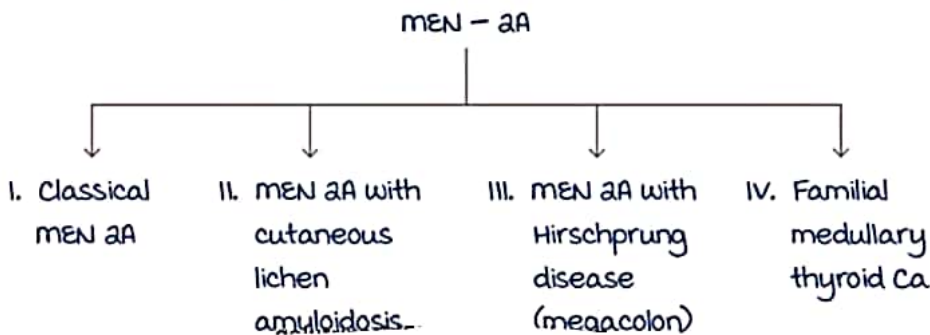
- **meningioma**

5) Pheochromocytoma (<0.05%)

MEN II syndrome

00:17:01

- **RET proto oncogene mutation (chromosome 10)**
- Autosomal dominant (m=F)
- Point mutation (**cysteine** → **Arginine**)



- Classical MEN 2A
 - 1) medullary thyroid Ca (**100%**)
 - marker → Calcitonin
 - FNAC for diagnosis
 - Near total thyroidectomy

2) Pheochromocytoma (**50%**)

- Bilateral
- MC : Benign

3) 1° hyperparathyroidism

- **Hyperplasia** > Adenoma

MEN 2B (MEN 3):



- 1) medullary thyroid cancer
 - 2) Pheochromocytoma
 - 3) marfanoid habitus
 - 4) mucosal & intestinal ganglioneuromatosis
 - 5) myelinated corneal nerve fibre
- megacolon (very rare)

MEN - 4

- Due to cyclin dependent kinase 1 B mutation
- 1) Parathyroid
- 2) Pituitary
- 3) Testicular / Ovarian tumor
- 4) Adrenal / renal tumor

MEON

00:24:26

- Multiple endocrine & organ neoplasia

I. Carney's complex

- PPKAR 1 α mutation
- Atrial myxoma
- Pituitary (GH) (or) Adrenal tumor
- Adrenal tumor is more common

II. VHL disease :

- VHL gene
- RCC
- Cerebellar hemangioblastoma
- Pheochromocytoma (malignant ↑)

III. McCune Albright syndrome

- Gs α mutation

- Polyostotic fibrous dysplasia
- Pituitary tumor (GH > Prolactin)

IV. NF - 1

- Neurofibromin mutation
- Optic nerve glioma
- Pheochromocytoma

V. Cowden syndrome

- PTEN (TSG)
- Hamartoma
- Adenocarcinoma breast
- Endocrine involvement - thyroid

VI. Hyperparathyroidism jaw tumor syndrome

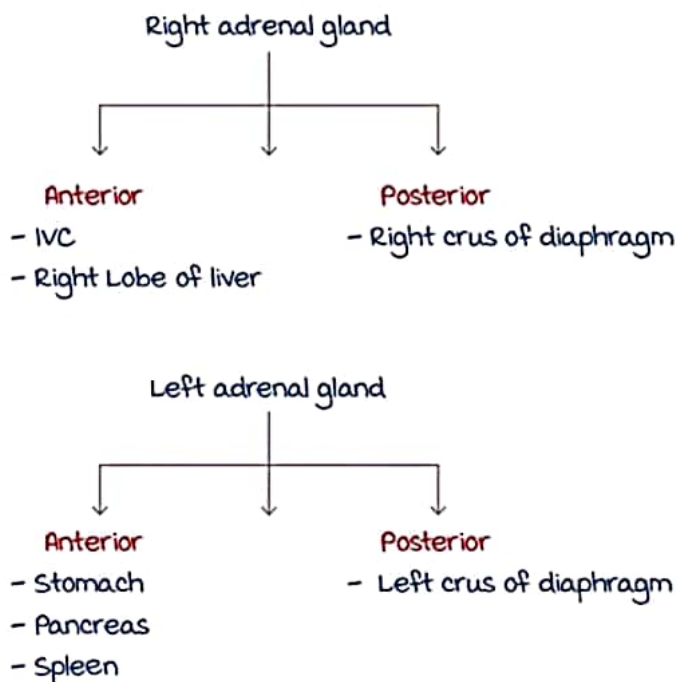
- Parafibromin mutation
- Jaw tumor
- ↑ PTH

ADRENAL CORTEX

- Adrenal cortex forms 80% of adrenal gland
- Adrenal medulla develops at 45 days of intrauterine life
- Adrenal cortex starts to develop towards the end of 2nd month (6-8 weeks) from coelomic epithelium (mesothelium) which invades the primordial medulla (neural crest)
- Hormone synthesis (cortisol) starts by 8-9 weeks
- Fetal cortex development is complete by 12 weeks
- In fetus, adrenal is bigger than kidney
Post birth, fetal cortex involutes and is replaced by adult cortex

Relations of adrenal gland

00:02:48



- Removal of adrenal is by laparoscopic retroperitoneal adrenalectomy
- Blood supply
 - I. Superior suprarenal → branch of inferior phrenic artery
 - II. Middle suprarenal artery → Direct branch of abdominal aorta
 - III. Inferior suprarenal artery → Branch of renal artery

Active space

Physiology

00:04:42

- I. Zona glomerulosa (15-20%)
 - mineralocorticoid (aldosterone)
 - II. Zona fasciculata (60-70%) [large lipid laden cells] ⊕
 - Cortisol
 - III. Zona reticularis (<10%)
 - Only after birth
 - Adrenal androgens
 1. Dihydroepiandrosterone (DHEA)
 2. Androstenedione
- Principal fetal adrenal hormone → DHEA
 - Aldosterone is not under any pituitary regulation, so even after hypophysectomy, levels are normal
 - Aldosterone is under the control of RAAS
 - Renin is produced by juxtaglomerular cells by 3 stimuli;
 1. Defective renal perfusion
 2. β_1 receptors
 3. PGE_2 , PGI_2
- Cortical collecting ducts
1. Principle cell (P cell)
 2. Intercalated cell (I cell)
- Aldosterone is not filtered but reaches basolateral membrane via peritubular capillary plexus
 - Binds to its receptor & activates protein inside cell
 - Protein inside P cell activates ENaC channel
 - ↓
 - 1. ENaC retains Na^+ , H_2O
 - 2. Aldosterone excretes K^+ , H^+
 - Hyperkalemia is due to renal failure unless proved otherwise
 - Hyperkalemia with renal function near normal or slightly deranged → Suspect aldosterone deficiency (adrenal insufficiency)

- Pseudohypoaldosteronism:
- Normal aldosterone levels but can't bind due to **fibrosis of tubules of kidney**
- ↓
- Renal tubular acidosis (type 4)

Zona fasciculata

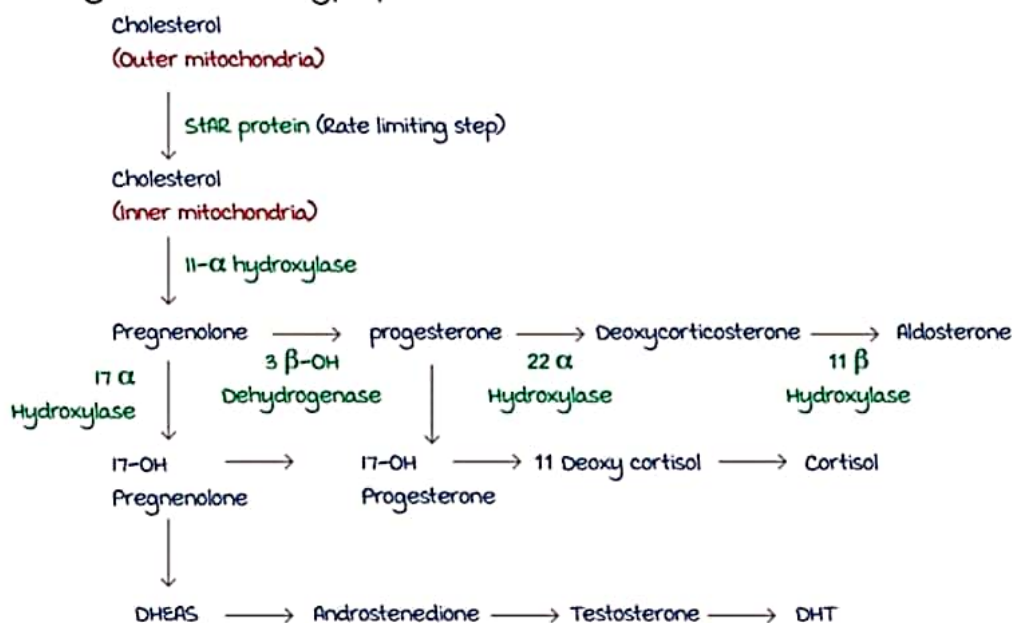
00:15:39

- Cortisol $\xrightarrow[11-\beta\text{-OH Steroid Dehydrogenase}]{}$ Cortisone
- Cortisol : both glucocorticoid & mineralocorticoid action
- Cortisone : Only glucocorticoid
- **Cushing syndrome** → Acquired deficiency of 11- β OH dehydrogenase deficiency

Zona reticularis:

- Secretes
 1. DHEA
 2. Androstenedione
- Functions →
 1. Axillary & pubic hair
 2. Libido

Congenital Adrenal Hyperplasia (CAH)



Active space

- mc deficiency $\rightarrow$ 21α hydroxylase
- 2nd mc $\rightarrow$ 11β hydroxylase
- 3rd mc $\rightarrow$ 17α hydroxylase
- 4th mc $\rightarrow$ 3β -OH dehydrogenase

ADDISON'S DISEASE

- Adrenal insufficiency
- 80% → Due to problem in adrenal gland
→ Primary adrenal insufficiency
- 20% → Due to problem in the pituitary
→ Secondary adrenal insufficiency
- Primary adrenal insufficiency:
 - Zona glomerulosa → Aldosterone ↓↓
 - Zona fasciculata → Cortisol ↓↓
 - Zona reticularis → DHEA, Androstenedione ↓↓
 - ACTH ↑↑
- Secondary adrenal insufficiency:
 - Low ACTH
 - ∴ Zona fasciculata } Cortisol low
 - Zona reticularis } DHEA ↓↓
 - Aldosterone normal

Etiology

00:02:54

- Primary adrenal insufficiency:
 - m/c/c (India): TB
 - m/c/c (Worldwide): Polyglandular autoimmune syndrome
(type 1, type 2) (autoimmune)
↓
AI hydroxylase autoantibodies
 - m/c infection (worldwide): Histoplasmosis
- secondary adrenal insufficiency:
 - m/c/c: Acquired hypopituitarism (most often cause: Tumors)

Primary adrenal insufficiency

00:05:52

- Cortisol ↓↓: Fatigue, asthenia, tiredness, loss of appetite, loss of weight, repeated episodes of hypoglycaemia and hypotension, euvolemic hyponatraemia
- Aldosterone ↓↓: Loss of salt and $H_2O \rightarrow$ Orthostatic hypotension
Giddiness
Dizziness
Salt craving
Hyperkalemia, hypovolemic hyponatremia
- ↓↓ DHEAs and androstenedione: Loss of libido
Dry skin
Decreased body hair
- ↑ ACTH: Widespread hyperpigmentation seen on skin and mucus membranes (spares tongue)

metabolic issues:

- 1) Hyponatremia
- 2) Hyperkalemia
- 3) Hypercalcemia
- 4) Hyperglycaemia
- 5) ↑ Mg^{2+}

Secondary adrenal insufficiency

00:10:49

- All features of cortisol ↓↓
Sex steroid ↓↓
- Aldosterone normal and ACTH ↓
- Other pituitary hormones ↓↓

	Primary adrenal	secondary adrenal
Etiology	TB, Autoimmune	Pituitary
GC deficiency	++++	++++
mc deficiency	+++	-----
Androgen deficiency	++++	++++
Salt craving, postural hypotension	++++	-----
Hyperpigmentation	++++	-----
Loss of axillary hair	++++	+++
Vitiligo	++++	-----
ACTH	High	High
S. potassium	High	N
S. Sodium	Low	N

- Primary adrenal insufficiency > 2° adrenal insufficiency
- Autoimmune > TB
- GC deficiency produces – Fatigue, weight loss, anorexia, hypoglycaemia
- mc deficiency – Hyponatremia, hyperkalemia, acidosis, hyperpigmentation
- Insidious in onset
- Fatigue / weakness/ Tiredness / Constipation / Abdominal Pain / Postural hypotension
- Hyperpigmentation (90%)
- Loss of axillary and pubic hair with dry itchy skin

Work up for Addison's

00:13:53

Screening test: 8 Am plasma cortisol



Ⓝ : >20 µg/dl

<3 µg/dl : Adrenal insufficiency

- Confirmatory test : ACTH stimulation test / Cosyntropin stimulation test / Synacthen stimulation test

↓
We give **250 µg** ACTH IV (or) IM

↓
Cortisol level after 1 hr

↓
Cortisol: **>20 µg/dl** : (N)
< 20 µg/dl : Addison's

- In CT: B/L asymmetrical adrenal enlargement (↑ ACTH)

↓
Finally may lead to atrophy

Electrolyte abnormalities

- Hyponatremia
- Hyperkalemia
- Hypercalcemia
- Hypoglycemia
- Hypotension

Management

00:18:11

- Chronic adrenal insufficiency: **Steroids**
(short acting hydrocortisone)
10 mg - 5 mg - 5 mg
(8-9 AM) (1-2 PM) (4-5 PM)
+
Fludrocortisone (50-100 µg)

Acute addisonian / adrenal crisis

00:19:15

- Causes:
 - Rapid tapering / non compliance to steroid
 - Any form of stress in a patient with adrenal insufficiency

- Presentation: Acute abdominal pain

+

Vomiting

+

Circulatory failure

Hypotension

Hypoglycaemia

- management: 3L of NS / Dextrose in NS

↓

Start IV hydrocortisone

100 mg IV Q6H x day 1

100 mg IV Q8H x day 2

50 mg IV Q8H on day 3

Convert to oral steroids

Children with adrenal insufficiency

00:23:03

- Causes:

1) Congenital adrenal hyperplasia (CAH)

2) X-linked adrenoleukodystrophy (↑↑ very long chain fatty acids)

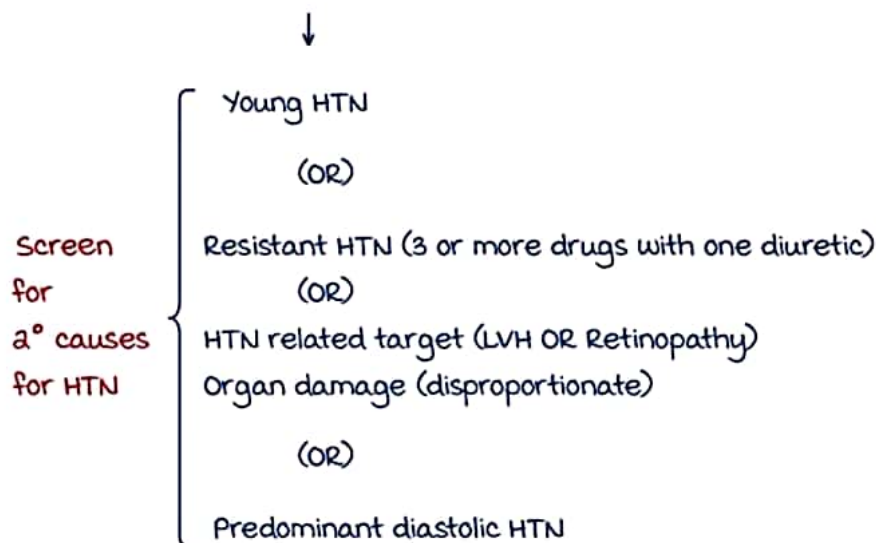
CONN'S SYNDROME

Primary Hyperaldosteronism (PHA)

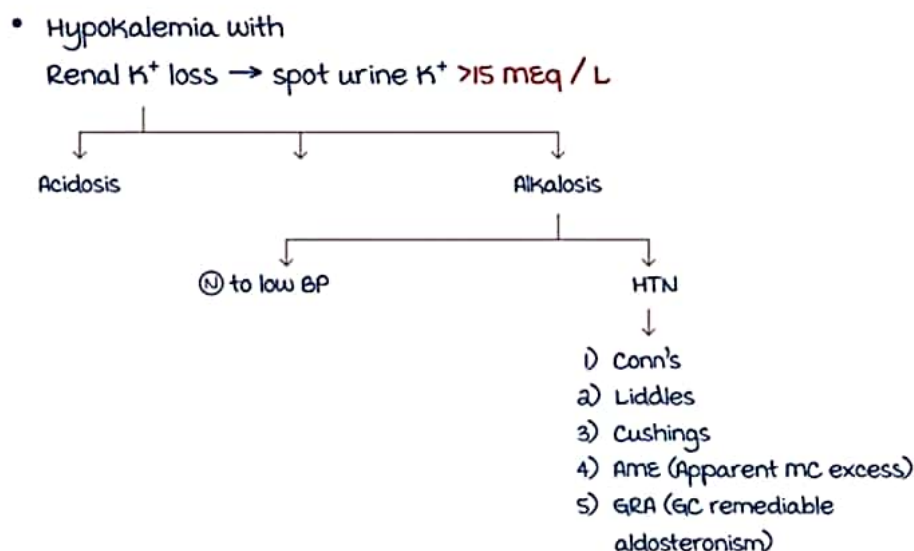
00:00:22

- 2 causes:
 - 60% : B/L adrenal hyperplasia
 - 40% : U/L adenoma } conn's syndrome
- Can occur in any age group
- m = F (>20 yrs)
- Aldosterone excess:
 - Salt and water retention → HTN (diastolic)
 - Loss of K^+ (Hypokalemia)
 - Loss of H^+ (Alkalosis)
 - No edema due to ↑ ANF (excrete Na^+)

Presentation: HTN (OR) hypokalemia



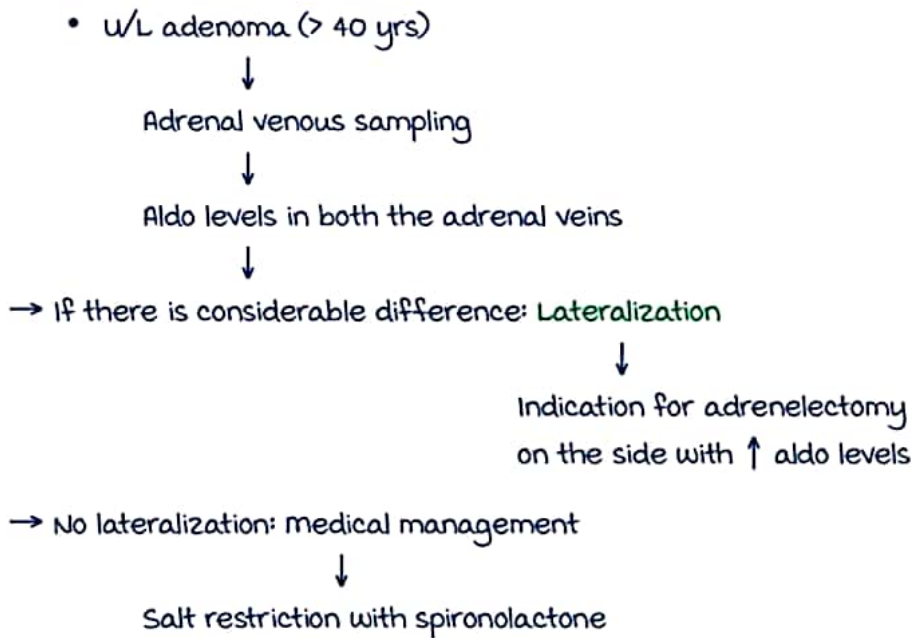
- 2 causes for HTN
 - Renal
 - Endocrine:
 - 1) Conn's (PHA)
 - 2) Liddle's
 - 3) Pheochromocytoma
 - 4) Cushing's



Work up for Conn's syndrome

00:11:42

- Screening test:
 - 1) Plasma Aldosterone concentration ($\uparrow\uparrow$) $> 10 \text{ mg/dl}$
 - +
 - 2) Plasma renin activity ($\downarrow\downarrow$) $< 1 \text{ mg/ml/hr}$
- Stop spironolactone 6 weeks before test
- If Ⓝ values while patient on ACE/ARB/ β -blocker/Diuretic, stop the drugs for 4 weeks and repeat the test
- Confirmatory test:
 - Done in patients with PAC $> 10 \text{ mg/dl}$ and PRA $< 1 \text{ mg/ml/hr}$
 - Saline infusion test
 - ↓
 - Infuse 2 l of NS over 4 hrs
 - ↓
 - repeat aldosterone $\rightarrow$ Still high (confirmatory)
- IOC: CT-abdomen visualizing adrenal gland
 - ↓
 - U/L adenoma (< 40 yrs) $\rightarrow$ U/L adrenalectomy
 - B/L hyperplasia $\rightarrow$ medical management
 - ↓
 - Aldosterone antagonist: Spironolactone (OR)
 - Eplerenone (free of gynecomastia)



Mendelian forms of genetic low renin HTN

00:22:18

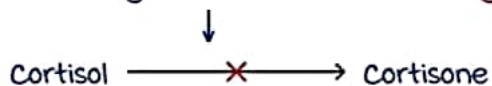
- | | | |
|-----------|---|---------------|
| 1) Liddle | } | - Hypokalemia |
| 2) AME | | - Alkalosis |
| 3) GRA | | - HTN |

Liddle

- Autosomal dominant
- Gain of function mutation of **ENAC**
 - ↓
 - Na^+ & H_2O retention → HTN
- K^+ and H^+ excretion : Alkalosis & Hypokalemia
- ⊖ RAS
 - ↓
 - Low renin
 - Low aldosterone
- Rx:- ENAC.
 - Amiloride
 - Triamterene

AME apparent mineralocorticoid excess

- Autosomal Recessive
- Deficiency of 11β -OH steroid dehydrogenase



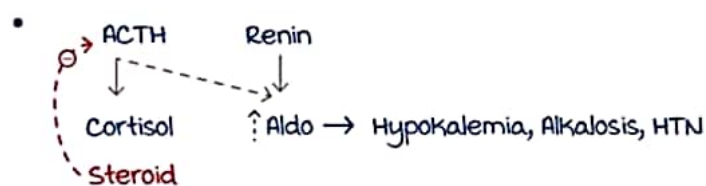
- $\therefore$ Cortisol accumulate

$\downarrow$
 MC + GC action
 $\downarrow$
 Hypokalemia
 Alkalosis
 HTN

- $\ominus$ RAS $\rightarrow$ Low renin
Low aldosterone
- Rx: Inhibit cortisol: Dexamethasone (inhibit ACTH)

GRA glucocorticoid-remediable aldosteronism

- AD
- m/c/c for mendelian low renin HTN



CUSHING'S SYNDROME

- Cortisol $\xrightarrow[dehydrogenase]{11-\beta \text{ OH Steroid}}$ Cortisone
- Acquired deficiency of 11 β OH steroid dehydrogenase
- Cortisol $\uparrow\uparrow$ (Hypercortisolism)
 $\downarrow$
mineralocorticoid + glucocorticoid action

Classification

00:02:08

- **m/c/c**: Iatrogenic
- Endogenous cushing syndrome :
 - **ACTH dependent (90%)**:
 - ACTH secreting adenoma of - **75%**
Pituitary (Cushings disease)
 - Paraneoplastic (Bronchial or Pancreatic carcinoids) - **15%**
 - medullary thyroid cancer
 - Small cell lung cancer
 - **ACTH independent (10%)**:
 - Adrenal adenoma - **5-10%**
 - Adrenal carcinoma - **very rarely**

Presentation

00:04:42

- Cortisol :
- Glucocorticoid action:
 - Carbohydrate metabolism
 - Fat metabolism
 - Protein metabolism
- Carbohydrate: $\uparrow$ gluconeogenesis
(adrenal diabetes)
- Fat: Redistribution of body fat → **Centripetal obesity**
Some lipolysis **Buffalo hump**

→ Protein: catabolic action and Anabolic action



1) muscle proteins broken down

Liver

→ Proximal myopathy

2) Bone → Severe osteoporosis / Short stature

3) Collagen → Purple striae

4) Defective platelet adhesion → Bruising, ecchymosis

5) Facial plethora

→ Sex steroid action :

Acne

Hirsutism

Amenorrhea

- Mineralocorticoid Action:

Hypokalemia

Alkalosis

HTN

• Can cross BBB → Psychosis or depression

Screening to be done in patients

1) Central obesity with protein catabolism

- Proximal myopathy

- Facial plethora, bruise and rarely purpura

- Violaceous stria due to loss of collagen

- Bruising & ecchymosis

2) osteoporosis at a young age

3) short stature with obesity and delayed BA

4) metabolic syndrome + Hirsutism due to ACTH

5) Incidental adrenal mass

1) Cardiac issues:

HTN → Atherosclerosis

Dyslipidemia

Diabetes

2) m/c menstrual abnormality → Amenorrhea

3) Blood abnormalities: ↑ WBC count, but still more prone to infection

Eosinopenia

4) Hypercoagulable state

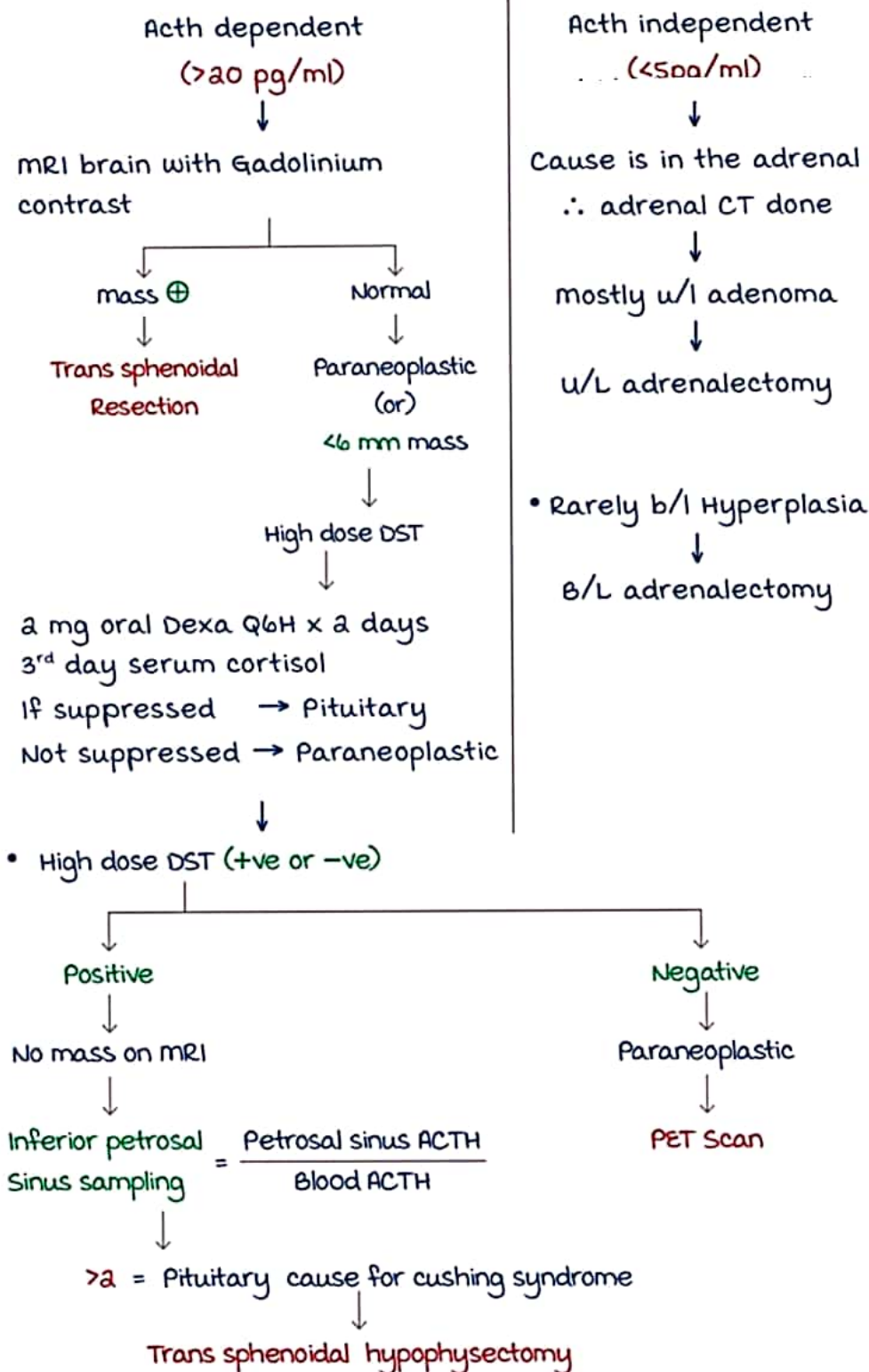
- Incidentaloma:
 - 90% of them are benign
 - Out of this 90%, 65-70% are endocrine inactive
 - Of the endocrine active incidentalomas,
 - m/c is Cushing's
 - 2nd is pheochromocytoma
- Features of malignancy on an incidentaloma:
 - 1) Size >4 cm
 - 2) CT density >20 HU
 - 3) CT contrast wash out <40%
 } Indication for U/L adrenalectomy

Work up for Cushing's

00:15:43

- Highly Sensitive Test: To rule out early → midnight serum cortisol
Cushing syndrome or (or)
mild Cushing syndrome
midnight salivary cortisol
- Highly specific test: To rule in PCOS / metabolic syndrome:
Overnight DST (dexamethasone suppression test)
(or)
Low dose DST
- Overnight DST: 1mg oral dexamethasone around 11 pm
↓
Cortisol level at 8 AM
Ⓝ : < 1.8 mg/dl
Cushing's: > 1.8 mg/dl
- Low dose DST: 0.5 mg oral Dexamethasone Q6H for 2 days
(more specific)
↓
3rd day morning 8 AM cortisol
Ⓝ : 1.8 mg/dl
Cushing: > 1.8 mg/dl
- Florid Cushing syndrome: Any test can be done
- In pseudo Cushing syndrome: Obese, alcoholic, depression
↓
hypercortisolism ++
Low dose DST
+
CRH stimulation (3rd day morning: 1mg/kg CRH i.v.)
↓
True Cushing: Cortisol will not be suppressed
If sr. cortisol < 1.8 mg/dl → Pseudo Cushing

- Part II of the work up: ACTH levels



Treatment

00:32:27

- Transsphenoidal surgery in Cushing's disease
- 75% remission rate
- Following which medical management done
 - DOC: Ketoconazole
 - Other drugs: Pasireotide
 - metyrapone
 - etomidate
 - cabergoline
- mitotane in adrenal cancer
- Fractional external beam radiotherapy in patients medically unfit for surgery
- B/L adrenalectomy only for B/L adrenal hyperplasia

Childhood Cushing's

00:34:22

- M >>> F
- Adrenal causes predominate
- Less protein catabolism
- Obesity & hypoglycaemia
- Precocious puberty
- Radiotherapy equally effective as surgery in children (for pituitary cause)
- Loss of diurnal variation in cortisol secretion is the first change in Cushing's

DIABETES : INTRODUCTION AND TYPES

Diabetes mellitus

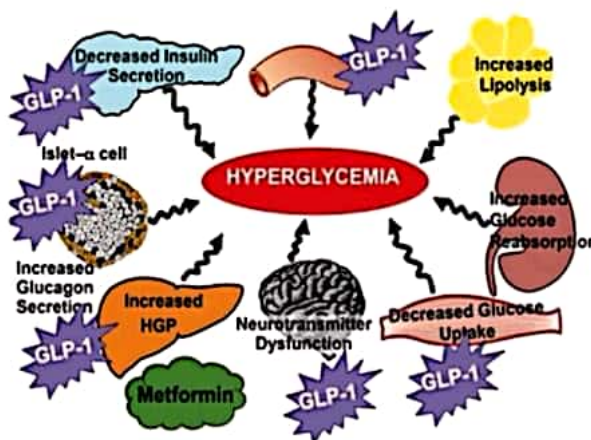
00:02:07

- mc Endocrinopathy
- Group of common metabolic disorders that share the phenotype of hyperglycemia

Ominous octet of DeFronzo

- **Pancreas:**
 1. ↓ Insulin secretion
 2. ↑ α -cell activity : ↑ Glucagon

(causes -pancreatic endocrinopathy - in type 2DM there is resistance to insulin in alpha cell-alpha cell proliferates-increased glucagon-hyperglycemia)
- **Liver:**
 3. ↑ Gluconeogenesis
- **Intestine:**
 4. ↑ Glucose absorption
- **Adipose Tissue:**
 5. ↑ Lipolysis
- **Kidney:**
 6. ↑ Glucose reabsorption (SGLT2)
- **Muscle:**
 7. ↓ Glucose uptake
- **Brain:**
 8. Neurotransmitter dysfunction



Criteria For The Diagnosis of DM (American Diabetes Association)

00:09:30

- FBS ≥ 126 mg/dl
- PPBS ≥ 200 mg/dl
- HBA_{1c} $\geq 6.5\%$
- RBS ≥ 200 mg/dl + symptoms

Type of Diabetes	Normal glucose tolerance	Hyperglycemia		
		Pre-diabetes*	Diabetes mellitus	
		Impaired fasting glucose or impaired glucose tolerance	Not insulin requiring	Insulin required for control Insulin required for survival
Type 1 Type 2 Other specific types Gestational Diabetes Time (years)				
FG	<5.6 mmol/L (100 mg/dL)	5.6-6.9 mmol/L (100-125 mg/dL)	≥7.0 mmol/L (≥126 mg/dL)	
a-h PG	<7.8 mmol/L (140 mg/dL)	7.8-11.0 mmol/L (140-199 mg/dL)	≥11.0 mmol/L (≥200 mg/dL)	
HbA1C	<5.6%	5.7-6.4%	≥6.5%	

Glycosylated hemoglobin

- 6 to 8 weeks control
- Best sensitivity and specificity for impaired glucose tolerance test (IGT)
- Value of HbA1C in
 - Anaemia - Falsely low
 - CKD-uremia - Falsely low
 - Thalassemia - Falsely low
 - Hereditary persistence of fetal Hb - Falsely low or high

Types of DM

00:16:22

Type 1.5 DM

It is of 2 types

- Ketosis Prone Diabetes (KPD)
- Latent Autoimmune Diabetes in Adults (LADA)

⇒ Ketosis Prone Diabetes (KPD)

- Patient with type -2 DM Presents as type -1 DM with Ketosis
- Also Known as Flatbush Diabetes

⇒ Latent Autoimmune Diabetes in Adults (LADA)

- Patient with type -1 DM presents as type -2 DM

Difference between type-1 DM & KPD, type 2 DM & LADA

00:23:32

Type - 1 DM with Ketosis	Ketosis Prone Diabetes(KPD)
• Autoantibodies present • No stigmata of insulin resistance • Lean ,tall, fair ,boys	• No autoantibodies • Insulin resistance present • Acanthosis nigricans, obesity,hirsutism, balanoposthitis

Type -2 DM	LADA
• No autoantibodies • Insulin resistance + • No feature of autoimmune illness	• Autoantibodies present • No feature of Insulin resistance • Feature of autoimmune illness-lean, tall, fair

LADA & KPD- Diagnosis

00:29:14

	LADA	KPD
• Age	Young adults (20-35)	Young adults (15- 25)
• Gender	male = Female	male > Female
• Presentation	Insidious	Explosive
• Body weight	Lean	Obese
• Ketosis	Uncommon	At onset
• Antibodies	+++++++	+
• Initial management	oral hypoglycemic agents(OHA)	Insulin
• Long term management	Insulin	OHA

- In KPD ⇒ Stigmata of insulin resistance (Acanthosis nigricans, balanoposthitis)
- ⇒ Dark, hirsute , obese male
- ⇒ Hyperinsulinemia → marker
- ⇒ LADA → lean, fair patients with stigmata of autoimmune illness

Current concepts in I.S Diabetes

- Careful quantitative measurements of GAD,ICA, IAA are required in all type -2

Active space

- Check for Fasting serum c-peptide and c-peptide response after 1mg glucagon administration
- Low fasting c - Peptide level indicates type - 1 DM
< 1.8 mg/dl after 1mg glucagon administration.
- c- peptide level is a measure of endogenous Insulin level

Endocrinopathies associated with diabetes

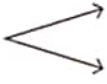
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1. Pituitary : Acromegaly
2. Adrenal cortex : Cushing syndrome, Conn's syndrome
3. Adrenal medulla : Pheochromocytoma
4. Thyroid : Hyperthyroidism
5. Parathyroid : Hyperparathyroidism
6. Pancreas : Glucagonoma, Somatostatinoma

PHYSIOLOGY OF INSULIN

Insulin

00:00:08

- Pancreas 
 - Exocrine: 98%
 - Endocrine: 02% → Islet of Langerhans
- α cells : Glucagon
- β cells : Insulin (maximum Number of cells)
- γ cells : Somatostatin
- F - cells : Pancreatic polypeptide

Insulin:

- Large protein (51 Amino acids)
- Polypeptide made up of 2 chains (21 AA and 30 AA) connected by disulfide bond
- Acts on tyrosine Kinase receptor

Metabolic effects

00:02:08

I. Carbohydrate metabolism

- Insulin dependent glucose uptake (GLUT - 4) in adipose tissue and muscle
- $\uparrow$ Glycogen synthesis and $\downarrow$ glycogenolysis
- $\downarrow$ gluconeogenesis in liver

⇒ In Insulin deficiency or Insulin resistance

- Hyperglycemia
- Glycosuria
- Osmotic diuresis (Polyuria, Polydipsia, polyphagia)

⇒ For every 100 mg/dl increase in blood glucose, serum Na^+ falls by 1.6 mEq/L

II. Lipid metabolism:

- Insulin keeps lipolysis under control
- Lipolysis occur with the help of enzyme hormone sensitive lipase
- Insulin inhibits hormone sensitive lipase

- In insulin deficiency or insulin resistance:

- $\uparrow$ lipolysis $\rightarrow \uparrow$ Free fatty acids (FFA)
- FFA enters liver and leads to $\uparrow$ gluconeogenesis, $\uparrow$ TG, $\uparrow$ VLDL and promote ketosis.

III. Protein metabolism:

- Insulin - anabolic hormone
- Insulin increases the uptake of amino acid
- Increases protein synthesis
- In Insulin deficiency or resistance $\rightarrow$ Negative Nitrogen balance
It leads to weakness, muscle wasting, susceptibility to infection

IV. Potassium Transport:

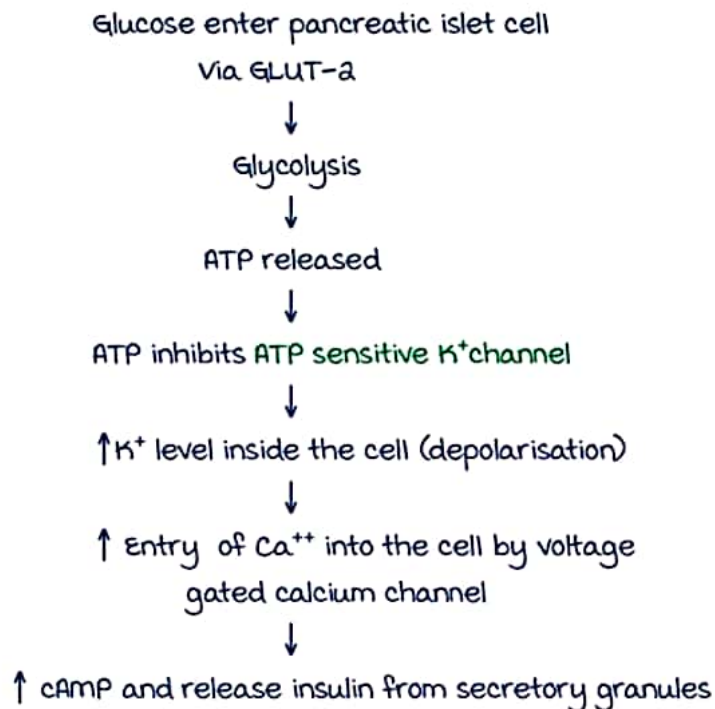
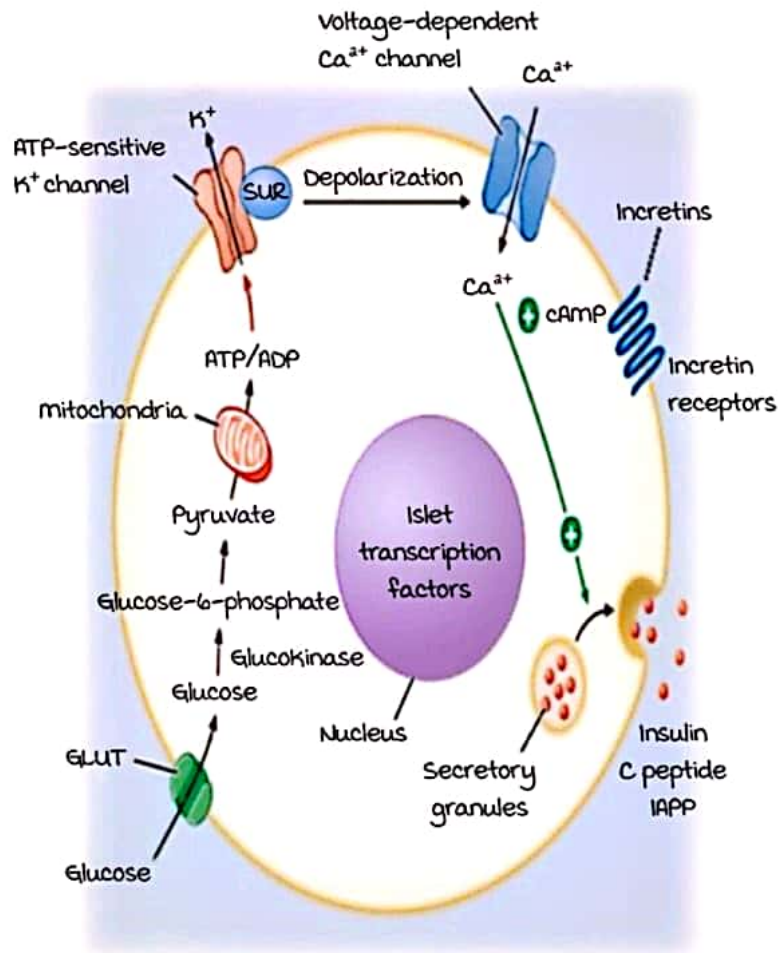
Insulin activates $\text{Na}^+ - \text{K}^+$ ATPase

K^+ enters into cell : Hypokalemia

metabolic defect	Chemical abnormality	Clinical abnormalities
Carbohydrate metabolism		
• $\downarrow \downarrow$ Glucose uptake by tissues (muscle, adipose tissue, liver) • $\uparrow \uparrow \uparrow$ Glucose production secondary to glycogenolysis and gluconeogenesis in liver	Hyperglycemia $\downarrow$ Glycosuria $\downarrow$ Osmotic diuresis	• Polyuria, Polydipsia, Polyphagia • Blurred vision • Diminished mental alertness • Dehydrated ($\rightarrow$ death)
Protein metabolism		
• $\downarrow$ uptake of amino acids • $\downarrow$ Protein synthesis • $\uparrow$ Proteolysis	• Negative nitrogen balance • $\uparrow$ Levels of branch chain amino acid • $\uparrow$ Blood urea nitrogen level • $\uparrow \text{K}^+$ level	• Weakness • Poor resistance to infections • muscle wasting
Lipid metabolism		
• $\uparrow$ Lipolysis • $\downarrow$ Lipogenesis • $\uparrow$ Triglycerides, FFA production • $\uparrow$ Ketone production • $\downarrow$ Ketone excretion • $\uparrow$ Production of LDL and VLDL	• $\uparrow$ Plasma FFA • $\uparrow$ Plasma glycerol • Hypertriglyceridemia • $\uparrow$ Plasma and urine ketone • $\uparrow$ Plasma LDL and VLDL	• Loss of adipose tissue $\rightarrow$ weight loss • Pancreatitis • metabolic acidosis $\rightarrow$ Hyperventilation $\rightarrow$ Kussmaul breathing $\rightarrow$ death • Atherosclerotic vascular disease

Mechanism of insulin release

00:11:44



- ⇒ Insulin is produced from **Rough Endoplasmic reticulum** and stored inside secretory vesicle of golgi apparatus
- ⇒ Insulin is released along with **C-Peptide** and islet associated **Pancreatic polypeptide (Amylin / IAPP)**
- ⇒ Drugs that inhibit ATP-Sensitive K^+ channel:
 - Sulfonylureas
 - meglitinide analogues: Repaglinide, Nateglinide

Glucose transporters

00:16:35

- GLUT-4** ⇒ Insulin dependent glucose uptake: Predominantly adipose tissue, muscle & heart
- GLUT -2** ⇒ Liver, β -cells of pancreas
- GLUT-1 and GLUT -3** ⇒ Brain, Placenta → Insulin independent
- GLUT -5** ⇒ Small Intestine- for absorption of glucose (Facilitated diffusion)
 - ⇒ Fructose is also transported by GLUT-5

Secondary Active Transport

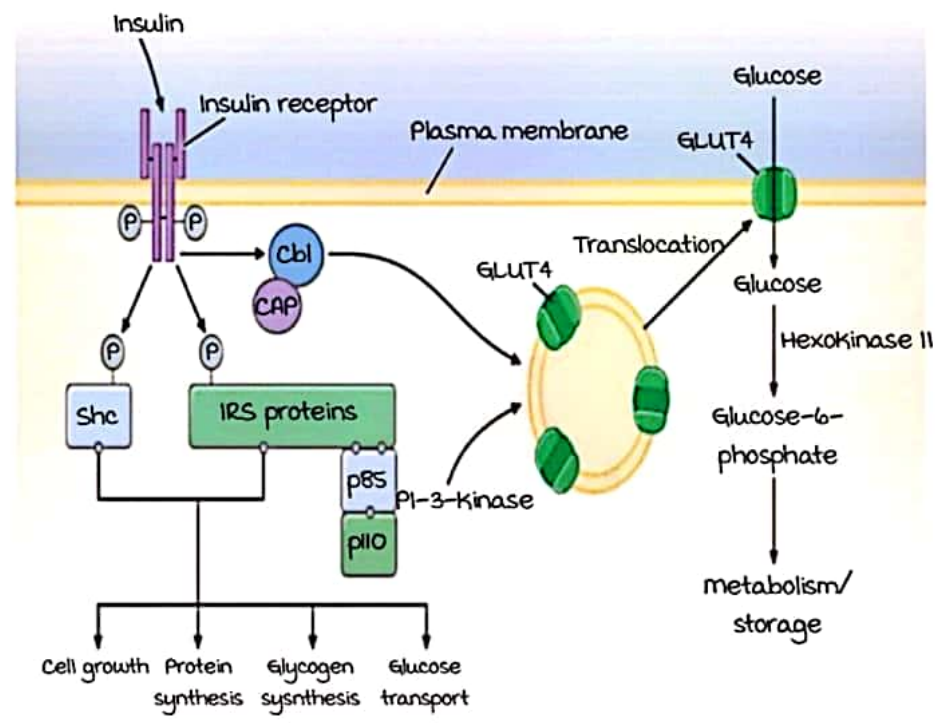
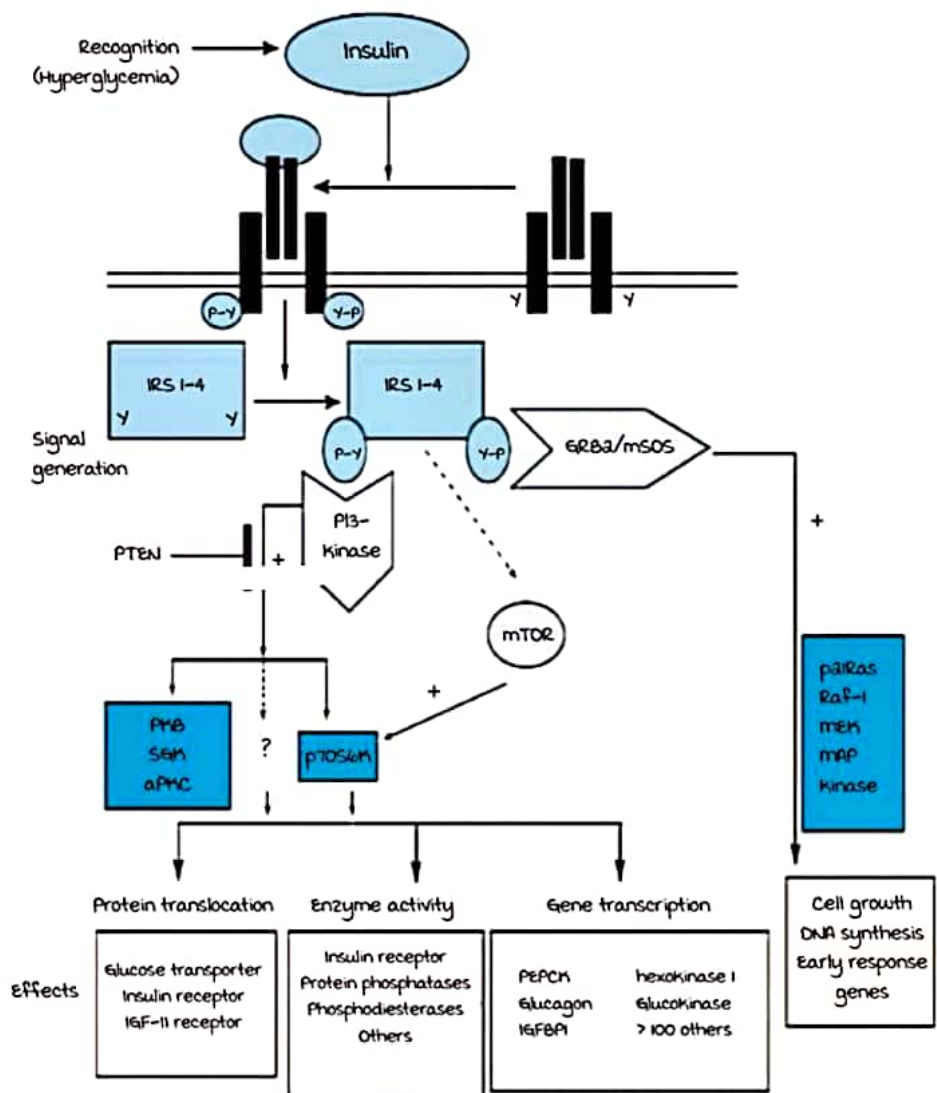
- **SGLT₁** : Present in small intestine
For glucose and galactose absorption
- **SGLT₂** : Present in proximal convoluted tubule in kidney
For sodium and glucose

SGLT2 inhibitors ⇒ Canagliflozin
Dapagliflozin
Empagliflozin

Mechanism of action

00:20:28

- Tyrosine Kinase receptor
- Intracellular dimerization occur
- Growth related properties of insulin mediated via PI_3 Kinase



Active space

Case scenario

1. Undetectable C- Peptide and high glucose $\Rightarrow$ Type 1 Dm
2. High levels of C-Peptide and blood glucose $\Rightarrow$ Type 2 Dm with insulin resistance
3. High level of C - Peptide and low glucose $\Rightarrow$ Insulinoma
4. Low levels of C-Peptide and low glucose $\Rightarrow$ Exogenous Insulin

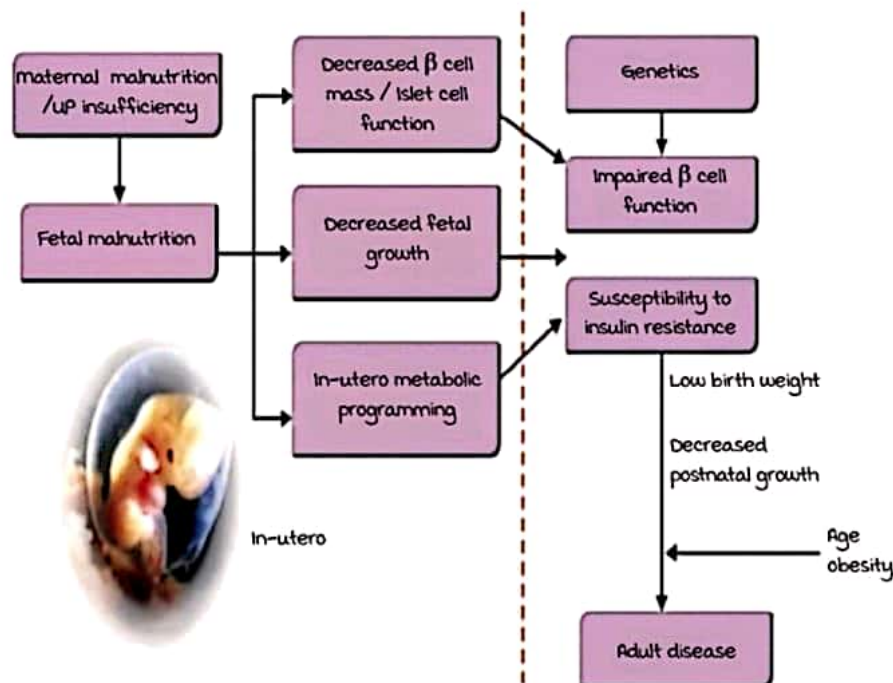
DIABETES CLASSIFICATION

Diabetes - pathogenesis

00:00:25

Thrifty Phenotype Hypothesis

- Feto maternal, uteroplacental insufficiency contributed by
 - maternal HTN hypertension(HTN)
 - maternal DM diabetes mellitus(DM)
 - Fetal malnutrition

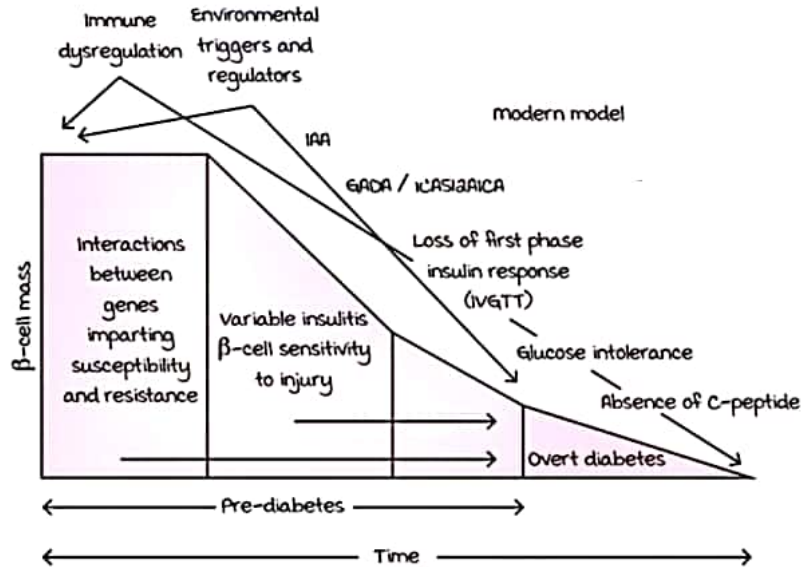


Type - 1 diabetes mellitus

00:03:52

- Immune dysregulation (autoimmune attack on β -cells [T-cell + B-cell])
- Pathology: Insulinitis
- Genetic susceptibility (influenced by low birth weight)
It is triggered by infections (rubella, mumps, coxsackie)
- Disease can develop at any age
- 70-80% beta cells are destroyed before the patient presents with Clinical manifestations
- **Honeymoon phase**
Period from 70% loss to 100% loss of cells during which patient may remain asymptomatic

- HLA association
 - MHC class 2 association
 - DQ $\Rightarrow$ Causative - DQA1, DQ5: DQB1, DQ8
 - DR $\Rightarrow$ Protective - DRB1, DR3
- Family history not significant
- Either parent having DM, chance of DM is 5%
- If both parent have DM, chance of getting DM is 15%
- Upto 50-70% concordance in identical twins



- Autoantibodies

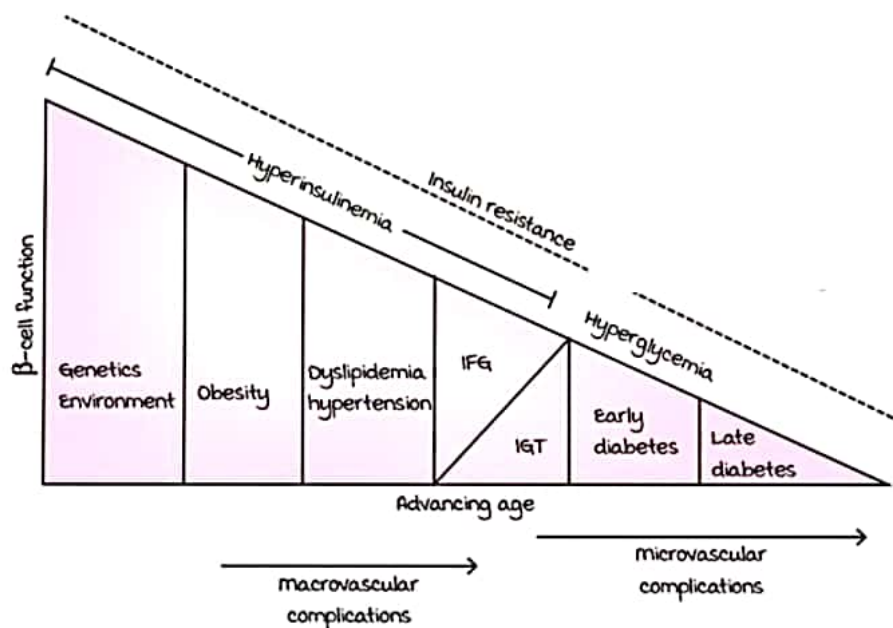
Table: Antibodies in type 1 diabetes mellitus (T1DM)

GAD	Exists in two isomeric forms GAD65 and GAD67, based on molecular weight most persistent autoantibody and is also useful in the diagnosis of LADA Catalyzes the conversion of glutamic acid to the inhibitory neurotransmitter GABA (γ-amino butyric acid)
IA-2A	member of the protein tyrosine phosphatase family and is a transmembrane protein Less common at T1DM onset Autoreactivity to the predominant c-terminal epitope of IA-2A is known as ICAS12 autoantibodies
ICA	Detected in 70-80% individuals with T1DM First antibody to appear in T1DM Declines in few years after diagnosis and about less than 5% of individuals remain positive for longer periods most difficult antibody to measure because ICA assays are subject to variations in pancreatic tissue, conjugate incubation time, etc. Reacts against sialoglyco conjugate, an insulinoma associated autoantigen
IAA	Is the only specific β-cell autoantibody most common in the new onset young T1DM than adults IAA determinations in serum are no longer valid once insulin treatment is initiated in patients with T1DM most difficult to accurately measure and reproduce
ZnT8A	Is a 369 AA, 6-transmembrane ZnT8 protein that concentrates Zn in insulin secretory granules The ZnT8 protein is encoded by SLC30A8 gene. Alleles of SLC30A8 have been shown to be also associated with T1DM

Types 2 diabetes mellitus

00:15:35

- Polygenic and multifactorial
- 70-90% concordance in identical twins
- Either parent having type - II DM, chance of getting DM is 25%
- Both parent having type - II DM, chance of getting DM is 40%
- HLA is less significant
- Insulin resistance followed by decreased secretion



Natural history of type 2 diabetes: Disease evolution

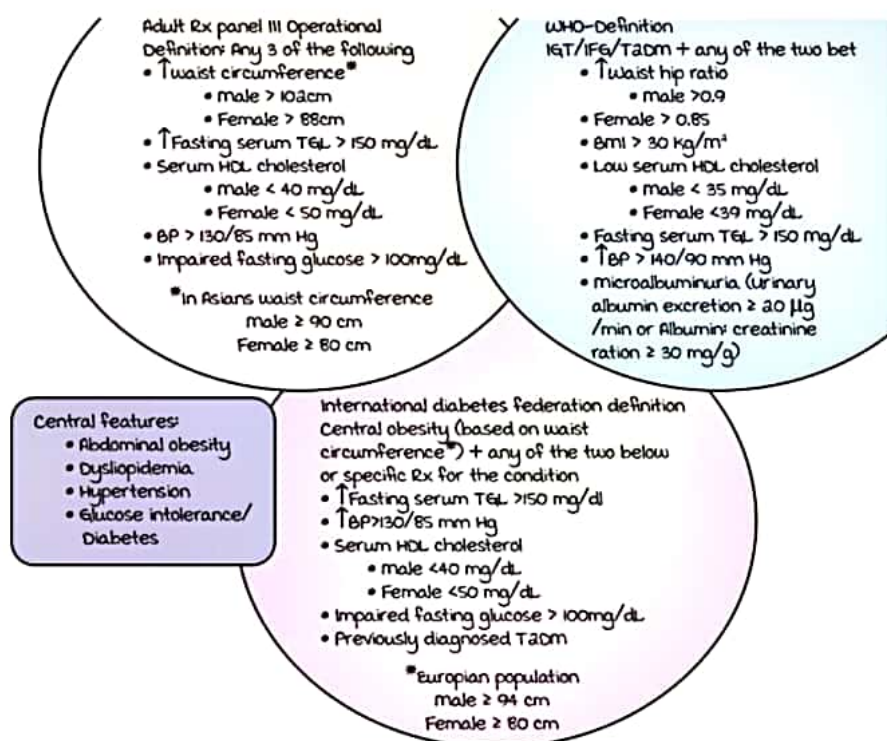
Metabolic syndrome

00:17:54

Adult Treatment panel III operational definition:

Any 3 of the following:

1. Waist circumference: male > 102 cm
Female > 88 cm
2. TG level > 150 mg/dl
3. HDL cholesterol: male < 40 mg/dl
Female < 50 mg/dl
4. Fasting blood sugar: > 100 mg/dl
5. BP > 130/85 mmHg



BMI

$$BMI = \frac{\text{Weight in Kg}}{(\text{Height in m})^2}$$

Parameter	WHO	INDIAN
Normal	18.5 - 24.9	18 - 22.9
Overweight	25 - 29.9	23 - 24.9
Obese	>30	>25

Diabesity/adiposopathy

00:22:02

- Diabetes + obesity

- There is ↑ CRP

↓ Adiponectin

- In central obesity, α receptors are changed to β₃

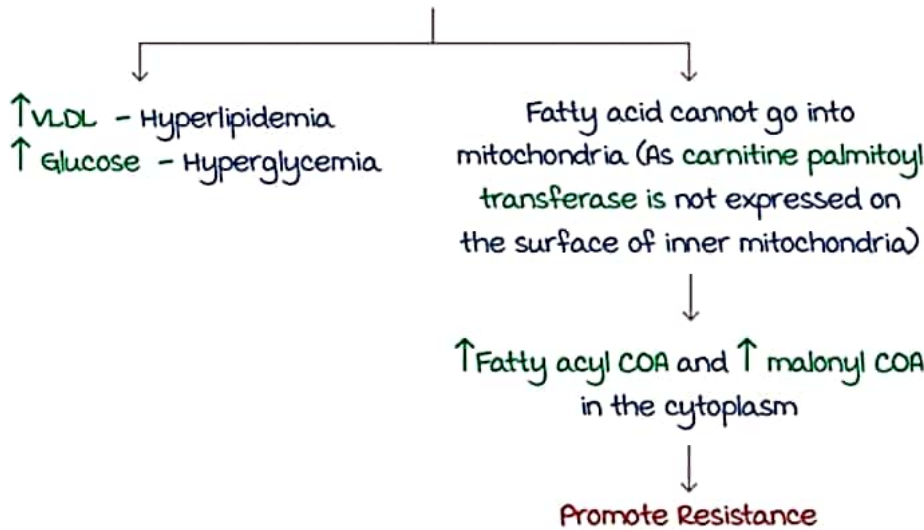


↑ Lipolysis



Free fatty acid (FFA) enters portal circulation and then into liver





- Hypertension
- Prothrombotic state
- Asian Indian phenotype

Type 1 DM vs Type 2 DM

TYPE 1 DM	TYPE 2 DM
- Younger	- Older
- Thinner	- Obese
- Family History rare	- Family History Common
- Weight loss	- Obese
- Osmotic symptoms - common	- Osmotic symptom- variable
- Low C peptide	- Higher C peptide
- No acanthosis nigricans	- Acanthosis nigricans +
- Dyslipidemia - - -	- Dyslipidemia + + +
- Hyperuricemia absent	- Hyperuricemia + + + +
- PCOS rare	- PCOS + + + +
- Antibodies ++	- Antibodies absent
- DKA- common	- DKA- rare

Note :

- In PCOS $\Rightarrow$ HAIR - AN Syndrome is seen
 $\Rightarrow$ Hyperandrogenism (HA), Insulin Resistance (IR) and Acanthosis Nigricans (AN)

- Genetic factors are more important in type - 2
- Insulin is increased in early Type -2 DM and normal later
- HLA DR3 and HLA DR4 In type -1 DM
- Early insulinitis is a feature of type - 1

Genetic syndromes with insulin resistance

00:28:50

1) Type A Syndrome

- Seen in young females (< 20 years)
- Defect in Insulin receptor (post receptor signalling)
- Characterized by obesity, Hyperandrogenism and acanthosis nigricans

2) Type B Syndrome

- 30-40 years females
- Antibodies against insulin
- Associated with other autoimmune illness

3) Rabson mendenhall Syndrome

- Seen in children
- Characterized by Acanthosis nigricans + nail changes + face and neck changes

4) Lipodystrophic DM

Genetic syndromes with diabetes

00:32:57

- Obesity related syndromes
 - Prader willi syndrome
 - Laurence-moon syndrome
 - Alstrom syndrome
- myotonic dystrophy
- Werner syndrome (progeria)
- Down syndrome
- Klinefelter syndrome
- Wolfram syndrome (Diabetes insipidus + DM + Optic atrophy + deafness)

Maturity Onset Diabetes of the Young (MODY)

00:34:35

- Autosomal dominant
- Adolescent or early adulthood (<25 years)
- male = Female

Types

Type 1 - HNF -4 α mutation

Type 2 - Glucokinase

Type 3 - HNF - 1 α

Type 4 - Insulin promotor factor

Type 5 - HNF - 1 β

Type 6 - Neuro.D,

Type 7 - KFL

⇒ All are transcription defect except **type - 2** (enzyme defect)

⇒ MC type most common(MC) type in India & worldwide = **Type 3**

⇒ **Type 2** MODY is seen in children (Type -2 does not require any drugs)

⇒ High risk for complication - **Type 5**

- No Stigmata of Insulin resistance
- No risk for micro / macro complications
- No risk for DKA
- Well controlled with Sulfonylurea's
- Insulin release is inappropriate for the degree of hyperglycemia
- Prognosis: Excellent
- Decreased SGLT₂ Receptors - Glycosuria + strong family history (3 generation involved)

Type - 3 diabetes

00:45:15

I. Type -3a DM

- Also Known as Hybrid diabetes
 - Double diabetes
 - Brain diabetes
- Alzheimers dementia

II. Type 3b diabetes

- Psychiatric drugs : SSRI ,Olanzapine
- Renal: Thiazide diuretic, Tacrolimus
- Endocrine drugs: Steroids, OCP, Growth hormone
- Anti - HIV drug: Protease inhibitors
- Oncology drug: L. Asparaginase

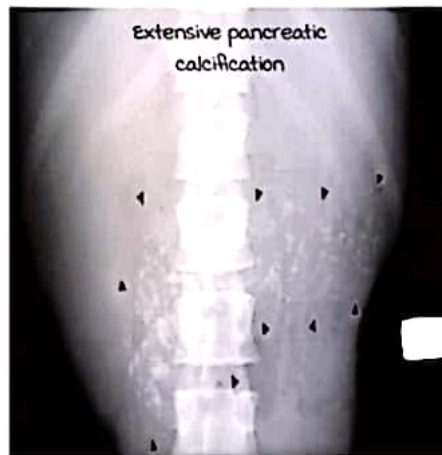
- vi. β - agonist
- vii. Diazoxide
- viii. CNS drug: Phenytoin

⇒ Drugs that cause diabetes independent of Insulin

- Nicotinic Acid
- Statin
- Aspirin

III Type 3C: Pancreatic diabetes

- Seen in
 - i) Fibrocalculous chronic pancreatitis
 - ii) Cystic fibrosis
 - iii) Hemochromatosis



- 15-25 years
- 70% male
- Present in catastrophic fashion
- Acute severe abdominal pain
 - +
Steatorrhoea
 - +
DM with
Extensive pancreatic calcification
- Risk of nephropathy
- Macro complications are rare

- Lean young
- Ketosis negative diabetes
- Gold standard for diagnosis - ERCP

	Tropical chronic Pancreatitis	Alcoholic chronic pancreatitis
Age and sex	2 nd & 3 rd decade: 70% male	4 th and 5 th decade mostly male
Alcohol Intake	usually Non - alcoholic	usually chronic heavy alcoholic
Nature & Incidence of diabetes	more aggressive, occurs in 90%	Slower, 50-60%
Pancreatic calculi	Large, discrete margins	Small, ill defined margin
Nature and location	Large ducts and marked dilation	Small duct and mild dilation
Fibrosis of gland	marked	Less severe
Risk of pancreatic cancer	Very High	Higher than in the general population

Type-4 diabetes

00:55:31

- Patient > 60 years developed hyperglycemia for the first time
- FBS < 200-250 mg/dl
- No features of insulin resistance
- No micro or macro complications
- Good prognosis
- Easily managed on oral hypoglycemic agents (OHA)
- ↑ T-regulatory cells [CD_3 , CD_4 , CD_{45} , Fox P₃ - marker]

New proposed classification of diabetes

00:59:23

Types of Diabetes	Autoantibody GAD	BMI	metabolic Control	Insulin deficiency or Resistance (HOMA - β & HOMA - IR)
SAID	Positive	Low	Poor	Insulin deficiency
SIDD	Negative	Low	Poor	Insulin deficiency
SIRD	Negative	High	Poor	Severe IR
MORD	Negative	High	modest derangements	mild or no IR

Type - 1 $\begin{cases} \text{SAID - Severe Autoimmune diabetes} \\ \text{SIDD - Severe insulin deficiency diabetes} \end{cases}$

Type - 2 $\begin{cases} \text{mild - MORD - mild obesity related diabetes} \\ \text{Severe - SIRD - Severe insulin resistance diabetes} \end{cases}$

Type - 4 $\rightarrow$ MARD - mild age related diabetes

Characteristics of type 1 and type 2 diabetes in children and adolescents			
Characteristics	Type 1	Type 2	MODY
Age at onset	Throughout childhood	Pubertal / Postpubertal	Pubertal / Post-pubertal
Gender	Female = male	Female > male	Female = male
Ethnicity	All (low incidence in Asians)	Native American African - American Hispanic	All
Onset	Acute Severe DKA common	Insidious Ketosis less common	Gradual Uncommon
Obesity	As in the population	Common	
Acanthosis nigricans	Absent	Present	Absent
Insulin secretion	Very low/absent	Variable	Variably decreased
Insulin sensitivity	Normal	Decreased	Normal
Insulin dependency	Permanent	Episodic	Infrequent
ICA (IA 20) Antibodies	70-80% ICA positive	ICA negative	ICA negative
GAD 65 Antibodies	40-70% GAD positive	GAD positivity $\pm$	GAD negative
Family history	5-15%	75-90%	100% Autosomal dominant
Mode of inheritance	Non - Mendelian, sporadic	Non - Mendelian, familial	

ACUTE COMPLICATIONS OF DIABETES

Intensive treatment (IT) / Lowering of glucose

00:01:03

Intensive glucose control trials			
	A1C goals	microvascular complications	macrovascular complications
DCCT/EDIC type 1 diabetes	<6.05%	IT reduced overall microvascular complications	Trend towards lower risk of CVD events with IT
UKPDS type 2 diabetes	(used FPG goals)	Relationship between glucose control and microvascular complications extended into range of normal A1c, with no glycemic threshold	10-Year post-trial follow-up: significant reductions in CVD outcomes and risk of nonfatal MI, stroke, or CVD death with IT
Advance type 2 diabetes	≤ 6.5% (IT) local guidelines (CT)	IT significantly reduced overall microvascular complications	
VADT type 2 diabetes	<6.0% (IT) planned separation of 1.5% (CT)	No significant reduction in microvascular complications with IT	No significant reduction in CV outcomes with IT
Accord type 2 Diabetes	<6.0% (IT) 7.0-7.5% (CT)	Terminated glycemic control study because of increased mortality in patients receiving IT with A1c <6%	

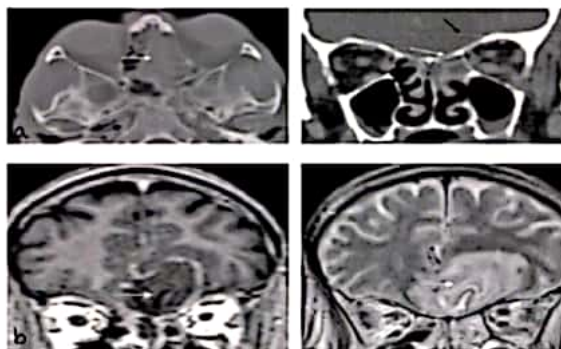
- IT with target HbA_{1c} 6.5% has found to significantly reduce microvascular complications and no significant ↓ in macrovascular complications

Infections unique to diabetes

00:03:53

1) Rhinocerebral mucormycosis:

- mucor / Rhizopus
- Angioinvasion with 'black necrotic turbinate' in diabetics
- Crosses cribriform plate of ethmoid
- Neurological complications ⊕
- IOC: MRI brain
- Doc: Liposomal amphotericin B
- Only oral azole used: Posaconazole

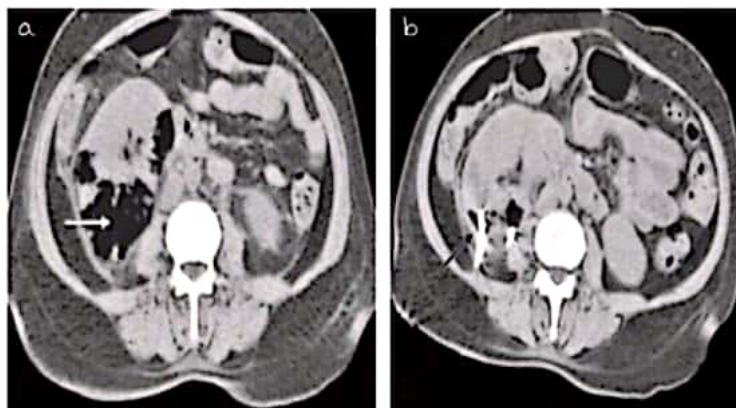


T1W and T2W MRI brain

II) malignant otitis externa:

- Pseudomonal, nocturnal ear ache
- Skull base paralysis, LMN cranial nerve palsy
- IOC: MRI
- DOC: Ceftazidime / Cefepime

III) Emphysematous pyelonephritis



- E. coli → Ferments glucose to produce gas
- Bad prognosis → High mortality
- IV antibiotics (medical management) superior
- Complicated UTI-like presentation

IV) Emphysematous cholecystitis:

- E. coli → Gas in gall bladder
- Clostridium
- Acute → surgical emergency → ∴ can produce gall bladder perforation, necrosis and gangrene
- Surgery carries 20% mortality risk
- Least mortality of aforementioned 4 conditions / Complications

→ melioidosis:

- Burkholderia pseudomallei
- In diabetics → weight loss, fever
- CT: multiloculated abscesses in liver and spleen

Acute complications – DKA and HHS

00:10:58

- DKA [Diabetic ketoacidosis]: Insulin deficiency + Glucagon / Counter regulatory hormone excess

→ Carbohydrate metabolism:

- ↓ Fructose 2,6 bisphosphate → Instead of glycolysis, gluconeogenesis happens
- Insulin-dependent glucose uptake due to GLUT 4 (adipose, muscle, heart) ↓

→ Protein metabolism:

- Proteolysis → Amino acid, lactate → Substrates for gluconeogenesis

→ Fat metabolism: ↑ HSL (Hormone Sensitive Lipase) → ↑ lipolysis

→ ↑ free fatty acid

- Substrate for gluconeogenesis
- ↑ VLDL
- Drawn into mitochondria [∴ Glucagon] → CPT [Carnitine Palmitoyl Transferase] expressed → β oxidation → ↑↑↑ acetyl CoA → ketone body pathway via HMG CoA → β hydroxyl butyrate
 - Acetone
 - Acetoacetate

- mcc of death in DKA (children): Cerebral edema

- DKA always has precipitation events:

- Infection
- Inadequate insulin
- Infarction
- Pregnancy
- Cocaine

- Presentation

- Uncontrolled nausea, vomiting
- Acute abdominal pain
- Acidotic breathing → disproportionate dyspnoea → Kussmaul's breathing
- Lethargy, obtundation
- ↑ HR, ↑ RR, ↓ BP/Postural hypotension

Management of DKA

00:23:59

- Investigations:
 - Patient catheterized → urine tested for ketone bodies
 - Rothera's test**: Cannot detect β - hydroxybutyrate
 - 2 peripheral blood lines placed → Blood sent for CBC, electrolytes, $S.Ca^{2+}$, $S.PO_4^{3-}$
 - ABG analysis
- Treatment
- **One peripheral line: Fluid replacement**
 - Average fluid required **9 l**
 - 3 l of NS over 1st 3 hrs
 - 3 l of NS over next 6 hrs
 - 3 l of $\frac{1}{2}$ NS / 5% D [if glucose <200] over next 12 hrs
 - **Bicarbonate replacement**: When pH <7.1
- **Other peripheral line:**
 - 0.1 U/kg of **regular insulin**, IV stat ⇒ 6/7U for 60-70 kg patient
 - 0.15 U/kg/hr infusion
 - For 50 kg patient
- 500 ml NS
25U insulin added
infused for 5hrs } **5U/hr** → For first 5hrs
- 500 ml NS
15U insulin
5hrs } **3U/hr** → For next 5hrs
- 500 ml NS
5U insulin
5 hrs } **1 U/hr** → For next 5hrs ⇒ Try overlapping here with **s.c.insulin**, which is continued later
- **Complication of treatment**: Hypokalemia, hypophosphatemia
⇒ To prevent for every 2 pint / 1 l NS → **add 1 amp KCL** = 10ml
1 ml = 2 mEq K^+ ⇒ 10 ml = 20 mEq of K^+

HONK / HHS

00:32:10

- HHS [Hyperosmolar hyperglycemic state] / HONK [Hyperglycemic hyperosmolar non-ketotic coma]
 - more in elderly
 - Definite intercurrent illness (+). Eg: URTI/LRTI
 - Presents in comatose state

Table - laboratory values in diabetic ketoacidosis (DKA) and hyperglycemia hyperosmolar state (HHS) (representative ranges at presentation)

	DKA	HHS
Glucose, mmol/L (mg/dL)	13.9-33.3 (250-600)	33.3-66.6 (600-1200)
Sodium, meq/L	125-135	135-145
Potassium	normal to ↑	normal
magnesium	normal	normal
Chloride	normal	normal
Phosphate	normal	normal
Creatinine	slightly ↑	moderately ↑
Osmolality (mosm/mL)	300-320	330-380
Plasma Ketones	++++	+/-
Serum bicarbonate, meq/L	<15 meq/L	normal to slightly ↓
Arterial pH	6.8-7.3	>7.3
Arterial PCO ₂ , mmHg	20-30	normal
Anion gap [Na-(Cl+HCO ₃)]	↑	normal to slightly ↑

- Severe hyperglycemia develops [>500 mg/dL generally]
- No counter-regulatory hormone excess → No ketosis
- Severe volume depletion → Acute volume correction → Can cause cerebral edema → ∴ slow correction / ½ NS preferable

CHRONIC COMPLICATIONS OF DIABETES

Microvascular complications

00:00:18

- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy

Diabetic nephropathy :

- Risk in T₁DM = T₂DM
 30-40%
 50-60% in India } Develop diabetic nephropathy
 - Control to be achieved in first 5 yrs
 - 'Nephron underdosing' at birth → mothers with HTN, DM
 - Pathogenesis:
 Uncontrolled hyperglycemia → alternate pathways of metabolism
 [Protein Kinase C ; Sorbitol ; Aldose reductase] → Growth factors,
 Cytokines → Afferent arteriolar vasodilatation → ↑ RBF, ↑ GFR
 → Hyperfiltration [stage I] → ↑ intraglomerular pressure →
 Normally dissipates; but, in
 Diabetes → Loss of renal autoregulation → intraglomerular HTN
 [1st major pathological change]
- ↓

Podocyte loss

↓

Parietal epithelium
begins to fuse with GBM

↓

Bowman space obliterated
→ synechiae formation
→ sclerosis

↓

Glomerulosclerosis

↓

proteins leak into urine (albumin)

↓

Potent tubulotoxic
→ Interstitial inflammation

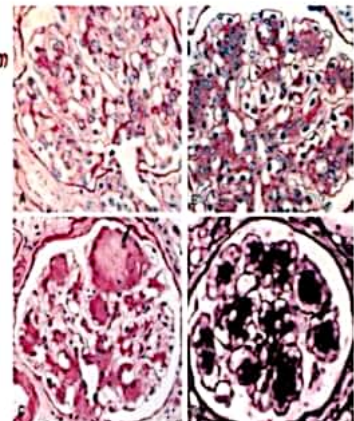
↓

TGF β → Fibrosis

↓

IFTA [Interstitial Fibrosis
Tubular Atrophy]

- Stage I:
 - "Hyperfiltration", ↓ in podocytes → endothelial dysfunction
- Stage II:
 - "Exercise induced microalbuminuria"
 - SHTN
 - Ambulatory PP widening
 - Absence of nocturnal dipping
- Stage III:
 - "Incipient diabetic nephropathy"
 - Microalbuminuria
 - Towards stage 3 end → Proteinuria
 - HTN starts
 - 3 pathological findings;
 - Earliest / universal finding → GBM thickening
 - mesangial expansion
 - Afferent and efferent arteriolar hyalinosis
- Stage 1+2+3 → ACEIs started → Can reduce proteinuria
- Stage IV:
 - "Overt diabetic nephropathy" → ↑ S.Creatinine
- Diffuse glomerulosclerosis : - 90% → due to diffuse mesangial expansion, non specific → degree of expansion 'always' correlate with renal failure
- Nodular glomerulosclerosis : - 50% → KW - Kimmelstiel-Wilson nodules → pathognomonic → due to presence of large asymmetrical nodules → number of nodules never correlate with renal failure
- Stage V:
 - "ESRD - End stage renal disease"
 - A/K/a IFTA - Gs
 - Non specific lesions:
 - Armanni - Ebstein lesions (due to tubular injury)
 - Capsular drops
 - Hyaline caps
 - Target HbA1c = 6.5 - 7%



→ T₂ DM patient, S. Creatinine = 1.5 mg/dl with diabetic nephropathy

$$GFR = \frac{(140 - \text{age}) \times BW}{72 \times S. \text{Creat}} = \frac{(140 - 60) \times 72}{72 \times 1.5} = \frac{80}{1.5} = 53 \text{ ml/min}$$

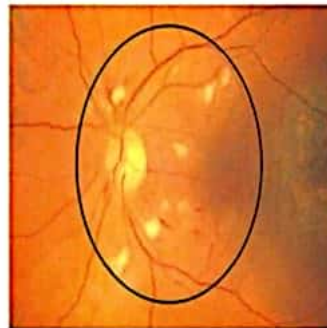
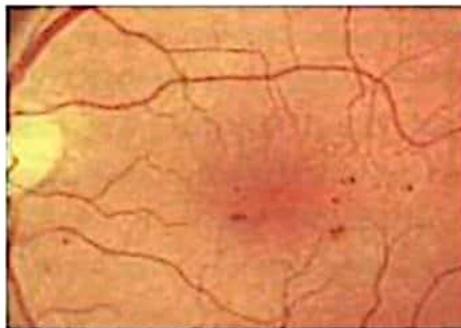
- Rate of fall of GFR in diabetic nephropathy = 8-10 ml/min/yr
⇒ ESRD [<15 ml/min GFR] in 4 yrs and becomes dialysis dependent
 - Anemia can independently ↑ rate of fall of GFR
- Indications of biopsy:
 - i) Absence of retinopathy in diabetics
[Retinopathy → 100% in T₁DM, 65-70% in T₂DM]
 - ii) Presence of edema → SGLT₂ receptor activation → Intra and extravascular edema; If edema ⊕ → Biopsy
 - iii) Frothing and proteinuria → If absent → Biopsy
 - iv) Systemic HTN → Absent → Biopsy
 - v) Presence of microscopic hematuria / Nephrotic syndrome
→ Biopsy
- Treatment:
 - metformin [contraindicated if GFR <40 ml/min]
 - Sulfonylureas → Glipizide; Glipizide
 - Linagliptin → Safe in renal failure
 - SGLT₂ inhibitors [contraindicated if GFR <30 ml/min]
 - GLP₁ agonist → Liraglutide safe in renal failure → cardiac benefits

Diabetic retinopathy

00:22:37

- Screening:
 - T₁DM : Once every 5 years
 - T₂DM : At diagnosis
- Types:
 - Non-proliferative [NPDR]: microaneurysm [earliest], hemorrhage, exudates, macular edema
[MCC for visual loss]
 - Proliferative [PDR]: "neovascularization", vitreous hemorrhage, retinal detachment

Non-proliferative stage



- Soft exudates/cotton wool spots: Pseudoexudates → Due to stasis of axoplasmic flow in outer nerve fibre layer

Skin manifestations in DM

00:24:29

- Necrobiosis lipoidica diabeticorum



- Scleroderma



- Acanthosis nigricans

- Diabetic dermopathy
[shin spots]



Measurement	Indication for Surgery ^{a,b}
Age	< 50 years
Serum calcium	> 1 mg/dL (> 0.25 mmol/L) above upper limit of normal
Bone mineral density	(a) T-score of ≤ -2.5 (osteoporosis) (b) Vertebral fracture on imaging study
Creatinine clearance	(a) Reduced to < 60 mL/min (b) 24-hour urine for calcium > 400 mg/day and increased stone risk by biochemical stone risk analysis (c) Nephrolithiasis or nephrocalcinosis on imaging study

- Granuloma annulare: Symmetrical papular, annular lesions distributed on arms → Have erythematous border and flat centre



Active space

Diabetic neuropathy

00:26:04

- $T_{2DM} > T_{1DM}$
 - Symmetrical polyneuropathies:
 - Distal to proximal, symmetrical sensory >> motor small fibre neuropathy
 - Rarely → Large fibre neuropathy
 - Spinothalamic tract involved
 - Focal and multifocal neuropathy:
 - Carpal tunnel syndrome
 - Mononeuritis
 - Pupil sparing 3rd nerve palsy (+)
 - Asymmetric lower limb motor neuropathy:
 - Diabetic amyotrophy
 - Mostly involves quadriceps
 - Autonomic neuropathy:
 - Postural hypotension
 - Erectile dysfunction
 - GI motility disorder
 - Gustatory sweating
 - Nocturnal diarrhea
-
- Small fibre neuropathy: C type; Pain, temperature; Hyperalgesia, constant burning; Gloves and stocking sensory loss; Deformities absent; motor deficit +; Tendon reflexes lost

→ Large fibre neuropathy: A delta type; Fine touch, vibration +; Sensory ataxia/ulcers; small muscle wasting +; motor deficit +++ ; Tendon reflexes lost ++++
-
- Drugs used:- TCA, Gabapentin, Carbamazepine, Duloxetine, SSRI

MANAGEMENT OF DIABETES

Treatment goals for diabetes

00:00:08

- HbA_{1c} : <7% [Ideal: 6.5-7%]
- FBS : 80-130 mg/dl
- PPBS : < 180 mg/dl
- BP : < 130/80 mm Hg
- LDL : < 100 mg/dl
- HDL :
 - Females : > 50 mg/dl
 - males : > 40 mg/dl
- TG : <150 mg/dl

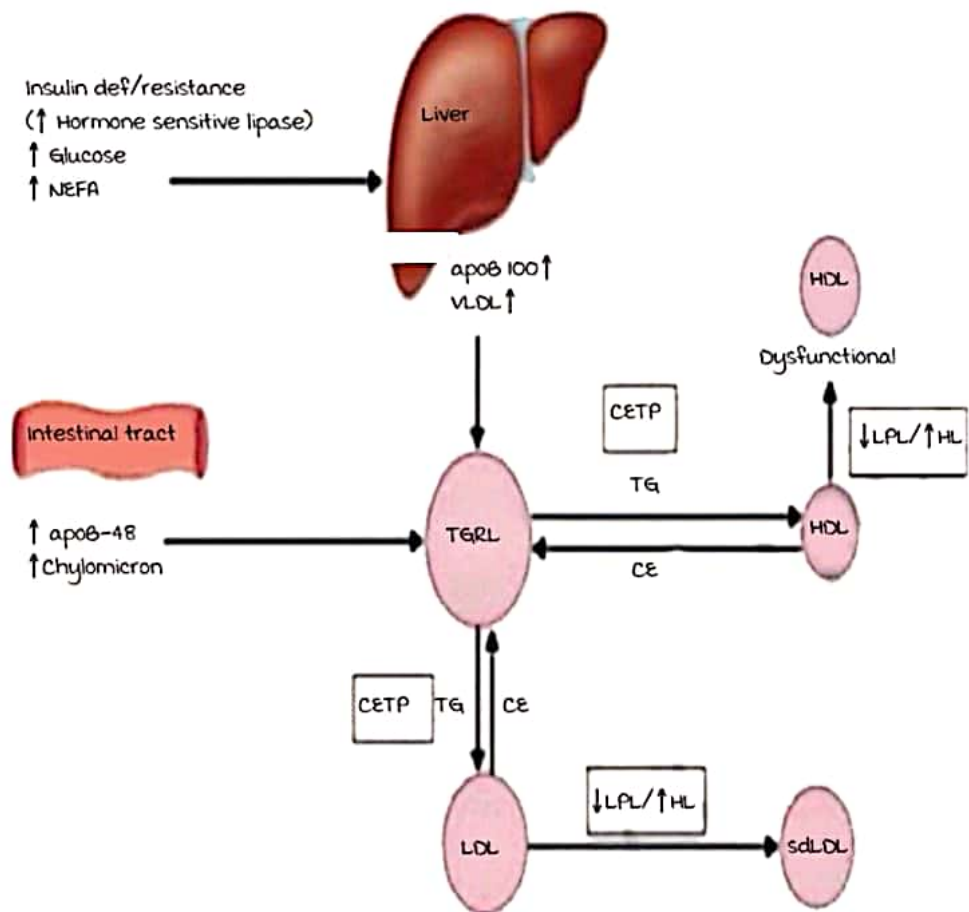
Diet and exercise

00:01:58

- Aerobic exercise: 5 times/week; Duration: 30-45 mins
- Carbohydrate: ↑ complex carbohydrate consumption:- Roti, Oats, fruits, whole wheat, vegetables; Fructose preferred over sucrose
- Protein:
 - 1g/kg protein
 - Class I protein:- Low fat milk, egg white, fish, soyabean, skinless chicken
- Fat:
 - No transfat; MUFA recommended; visible fat added while cooking ;
 - 3 tsp - 5 tsp [refined oil or cheese]

→ Lipid level in diabetes:

- Total cholesterol ↑
- VLDL ↑, Apo B 100 ↑
- TG ↑↑
- HDL: Low
- LDL: Normal
- Small dense LDL : ↑ atherogenic



DIABETIC DYSLIPIDEMIA

00:08:52

• management:

- Age <40 yrs
 - Non-atherosclerotic → Saroglitazar
 - Atherosclerotic vascular disease → Saroglitazar + statin
- Age >40 yrs → non atherosclerotic vascular disease → Saroglitazar + Statin

- Doc for diabetic dyslipidemia → Saroglitazar [dual peroxisome proliferator – activated receptor – (PPAR) α and γ agonist]
- If no ASVD, target LDL to be achieved is <100 mg/dl and if there is ASVD, target LDL = <70 mg/dl
- To achieve target, statin + Ezetimibe small PCSK9 inhibitors can be used
- Statins used: Atorvastatin: 40–80mg; Rosuvastatin: 20–40 mg

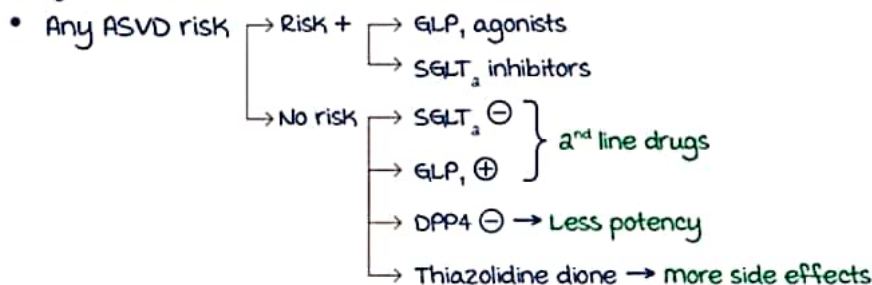
Drug therapy

00:14:30



- Apart from above conditions; OHAs (Oral hypoglycemic agents) started
- Biguanides :**
 - metformin (biguanide of choice) 500 mg BD [3 g maximum dose]
[1 g maximum dose as single drug]
 - MOA:
 - ↑ activity of AMP kinase and thus decreasing hepatic glucose production
 - ↑ $GLUT_4$ mediated glucose uptake in skeletal muscle, heart and adipose tissue
- **Advantages:**
 - Combats insulin resistance
 - Potency: HbA_{1c} reduction potential = 1.5-2%
 - Weight loss ⊕
 - No hypoglycemic risk
- **Disadvantages:**
 - Renal excretion unchanged [C/I in $GFR < 40ml/min$]
 - If used in RF → Cause lactic acidosis
 - Vit B_{12} deficiency

→ $HbA_{1c} < 7\%$ if not achieved with metformin;



- **SGLT₂ ⊖:**
 - Na⁺ dependent $GLUT_2$ ⊖
 - Dapagliflozin (5 mg or 10 mg), empagliflozin, canagliflozin

- Advantages:
 - Weight loss; SBP ↓; No hypoglycemia risk
 - Potency: 1-1.2%
 - Cardioprotective → mostly for empagliflozin
- S/E's:
 - Genitourinary infections → Especially *Candida*
 - ↑ risk for osteoporosis: ↑ LDL
 - ↑ risk of ketosis

Other OHAs

00:28:55

- **Sulfonylureas:**
 - ATP sensitive K^+ channels ⊖
 - Long acting sulfonylureas (Glibenclamide) disadvantages:
 - Hypoglycemic risk
 - Weight gain
 - Cardiac safety
 - Advantages: Potency 1-2%; Cheap
- **Gliclazide** [Only sulfonyl urea approved]:
 - ⊖ Platelet aggregation
 - Anti-oxidant action ⊕
 - Prevents endothelial injury
 - Cardioprotective
 - Prevents weight gain
 - 80 mg → 320mg dose
 - Safe in renal failure or glipizide 5 - 10 mg
- **Meglitinide analogues:**
 - HbA_{1c} reduction potential 0.5%
 - Nateglinide, repaglinide
 - Used for post prandial hyperglycemia
- **Thiazolidinediones:**
 - Pioglitazone; PPAR γ agonist
 - Combats insulin resistance

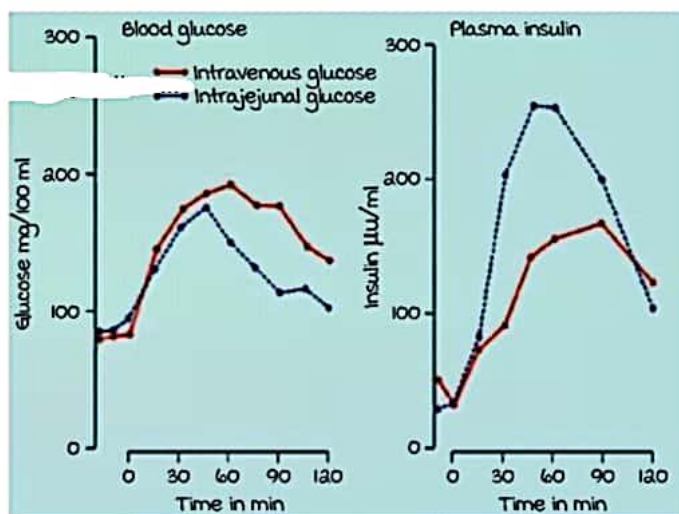
- Enhance glucose uptake via GLUT₄
- Potency: 0.5 - 1.4T
- S/E: weight gain, edema, bone #, ↑ risk of CA bladder

• α - glucosidase $\ominus$:

- Acarbose, voglibose, miglitol
- Anti-hyperglycemic
- S/E: Abdominal discomfort and belching

Incretin effect

00:39:02



Effect of incretin hormones

- IV glucose v/s oral glucose: Amplification of insulin release due to hormones produced from GIT
- Due to 2 hormones;
 - GLP-1 [Glucagon like peptide - 1]
 - GIP [Glucose dependent insulinotropic polypeptide a/k/a gastric inhibitory polypeptide]
- GLP-1 and GIP act on pancreas → ↑ β cell responsiveness → **Augment insulin release**
- They have extremely short $T_{1/2}$
 - GLP - 1 → 1-2 mins
 - GIP → 5-7 mins
- Rapidly degraded by DPP-4 [Dihydro peptidyl peptidase - 4]

Source : GLP-1 : L cells of ileum & colon

GIP - K cells of jejunum

GLP-1 is more potent than GIP

- **GLP-1 is superior to GLP**
 - Suppresses glucagon release
 - Delays gastric emptying
 - Activates satiety centre → associated with weight loss
 - But, it stimulates β cell expansion pancreatic disorders
- **Recombinant GLP-1**
 - Not degraded by DPP-4
 - Given s.c
- **DPP-4 inhibitors:**
 - Given orally
 - $\uparrow$ Physiological $T_{1/2}$ of GLP-1 and GLP

	GLP-1	GLP
Source	L cells / ileum & colon	K cells / jejunum
Glucose dependent insulin release	+++	+++
Enhances beta cell glucose responsiveness	+++	+++
Suppresses glucagon release	+++	---
Stimulates beta cell expansion	+++	----
Inhibition of gastric emptying	+++	---
Enhances satiety	+++	-----
Reduces body weight	+++	---
Half life	1-2min	5-7min

- **Recombinant GLP-1 analogues:** Eg: Exenatide, liraglutide, semaglutide
- Liraglutide is preferred → Long acting, given OD, dose 0.6mg
- **Advantages:**
 - Potency: 1-1.2%
 - Promote weight loss (act on satiety centre)
 - Suppresses glucagon
 - Inhibits gastric emptying
 - No risk for hypoglycemia
 - Cardiovascular benefit

- S/E's:
 - Nausea, vomiting
 - Acute pancreatitis
 - medullary thyroid cancer

Gliptins

00:49:48

- It is DPP4 $\ominus$; Prolongs physiological $T_{1/2}$ of GLP-1 and GIP
- Advantages:
 - Weight neutral drug [no weight loss/gain]
 - No hypoglycemia
 - Cardio-neutral drug [no cardiac toxicity / benefit]
- Disadvantages:
 - Cost
 - Potency 0.5-0.75% ; pancreatitis

	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Dose	100	50mg bd	5	25	5mg
Half life	Long	Short	Short	Long	very long
Frequency	Once	Twice	Once	Once	Once
Active met	No	No	Yes	No	No
Protein binding	Yes	---	---	---	HIGH
Renal	Yes	Yes	Yes	Yes	NO
Drug interactions	NO	NO	Yes	NO	NO

	GLP-1	DPP-4
mode of administration	s/c	oral
mechanism	GLP-1	GLP-1 and GIP
Augmenting insulin release	+++++	+
Suppressing glucagon	++	++
Hypoglycemia	-----	-----
Gastric emptying	delayed	-----
Weight loss	Yes	no
Nausea	Yes	no
Cardiovascular benefits	-----	-----

Amylin agonist

00:56:46

- **Pramlintide:**
 - Given S.C
 - Approved for both Type 1 DM and Type 2 DM
 - Hypoglycemia risk ⊕
 - Dose: 15mg prior to meals
 - Advantages: → ↓ glucagon, slows gastric emptying, improves satiety

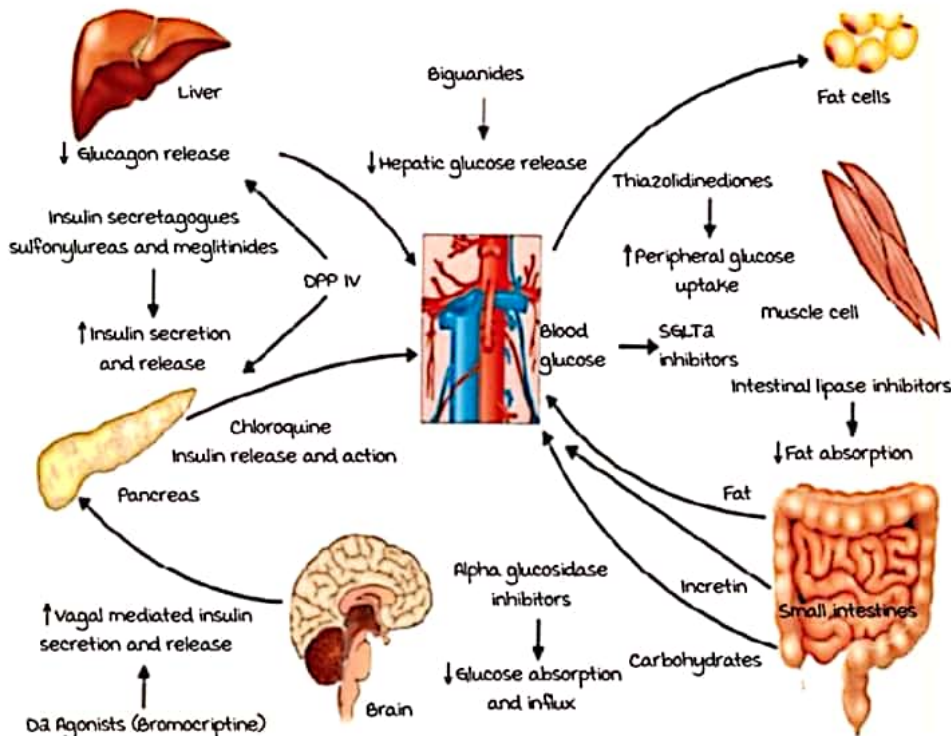
Newer drugs

00:57:50

- **Colesevelam** : Bile acid sequestrant
- **Lorcaserin** : 5HT_{2C} antagonist
- **Imeglimin** : Oxidative phosphorylation blocker
- **Telmisartan** : Only ARB acting on PPARγ
- **Ruboxistaurin** : Protein Kinase C inhibitors
- **Epalrestat** : Aldose reductase inhibitors
 - Bromocriptine, HCQ yet to be approved

Mechanism of action of OHA – summary

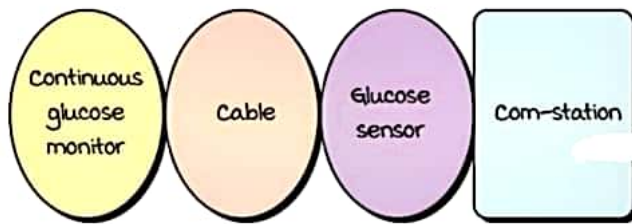
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mechanism of action of oral antidiabetic agents (OAHs)

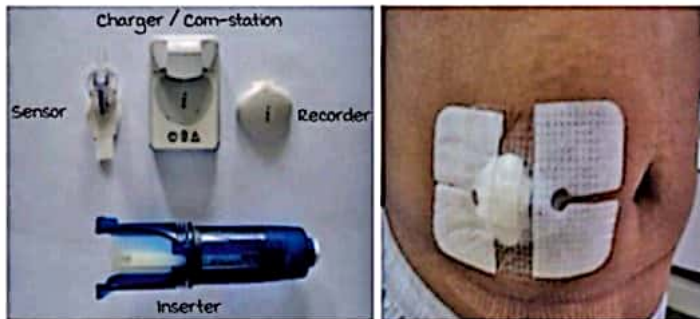
(SGLT2: Sodium glucose cotransporter 2; DPP-IV: Dipeptidyl peptidase 4 inhibitors)

INSULIN THERAPY IN DIABETES



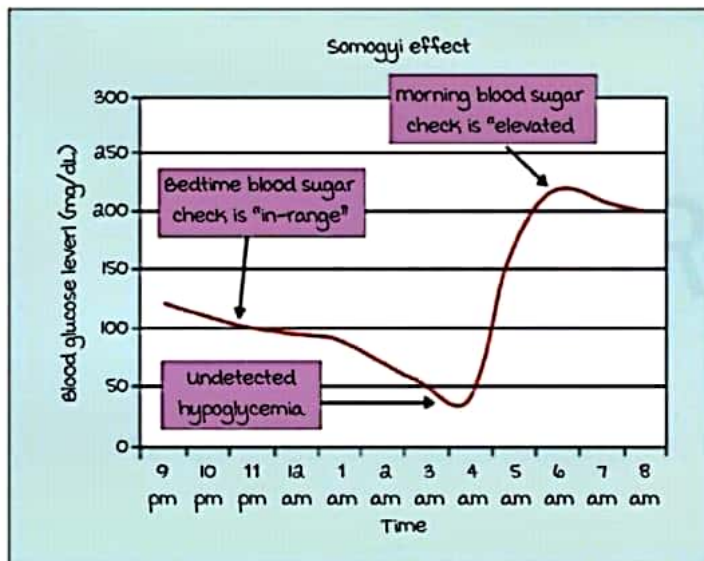
Components of continuous glucose monitoring system (CGMS)

Continuous blood glucose monitoring system



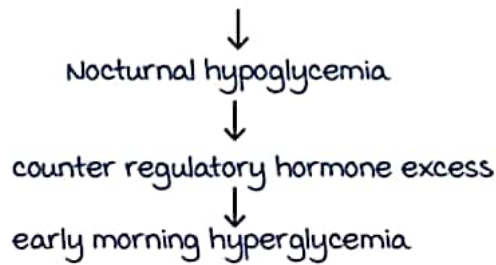
Flash glucose monitor

Continuous glucose monitoring system

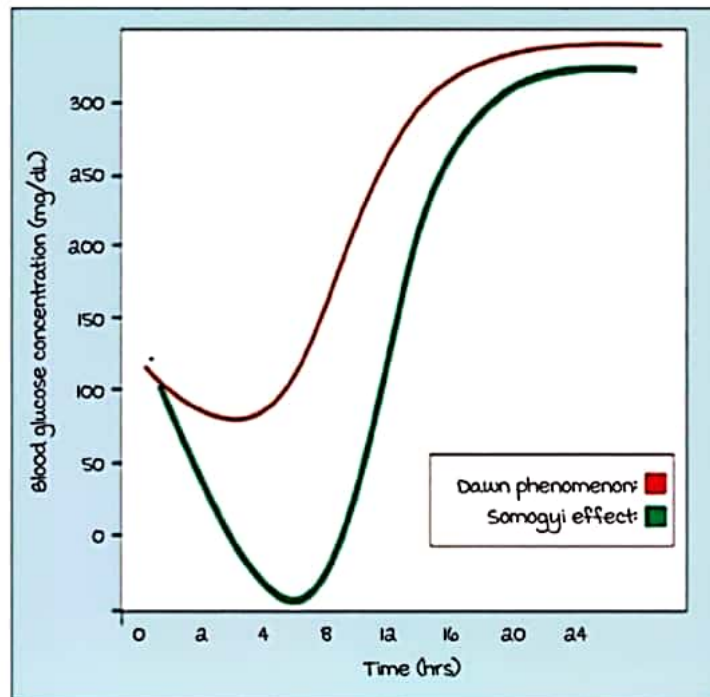


Active space

somogyi effect causes : excess night dose of insulin



Dawn phenomenon

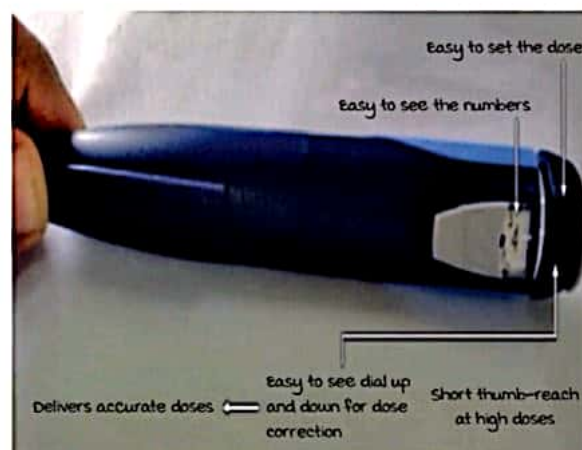


- cause : due to inadequate night dose of insulin

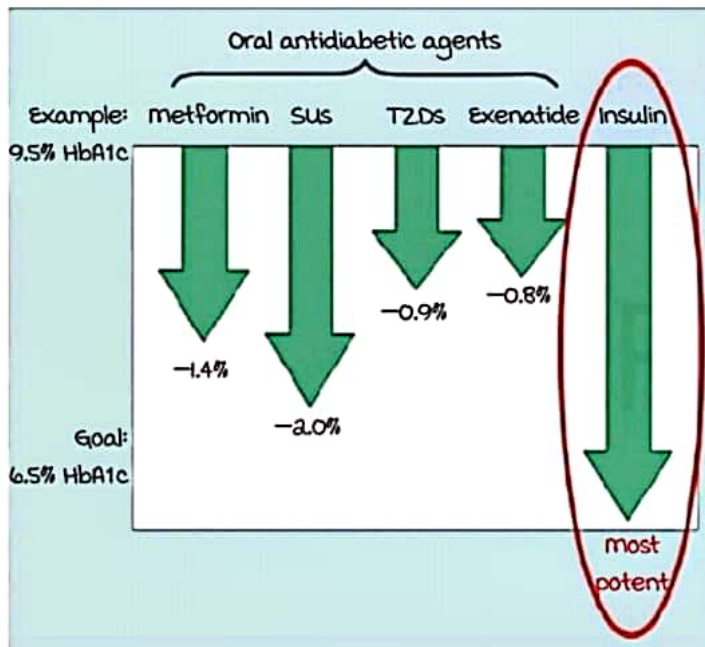
↓
Early morning hyperglycemia

- Night dose of insulin to be ↑↑ increased in dawn
↓↓ decreased in somogyi

pen insulin



Active space

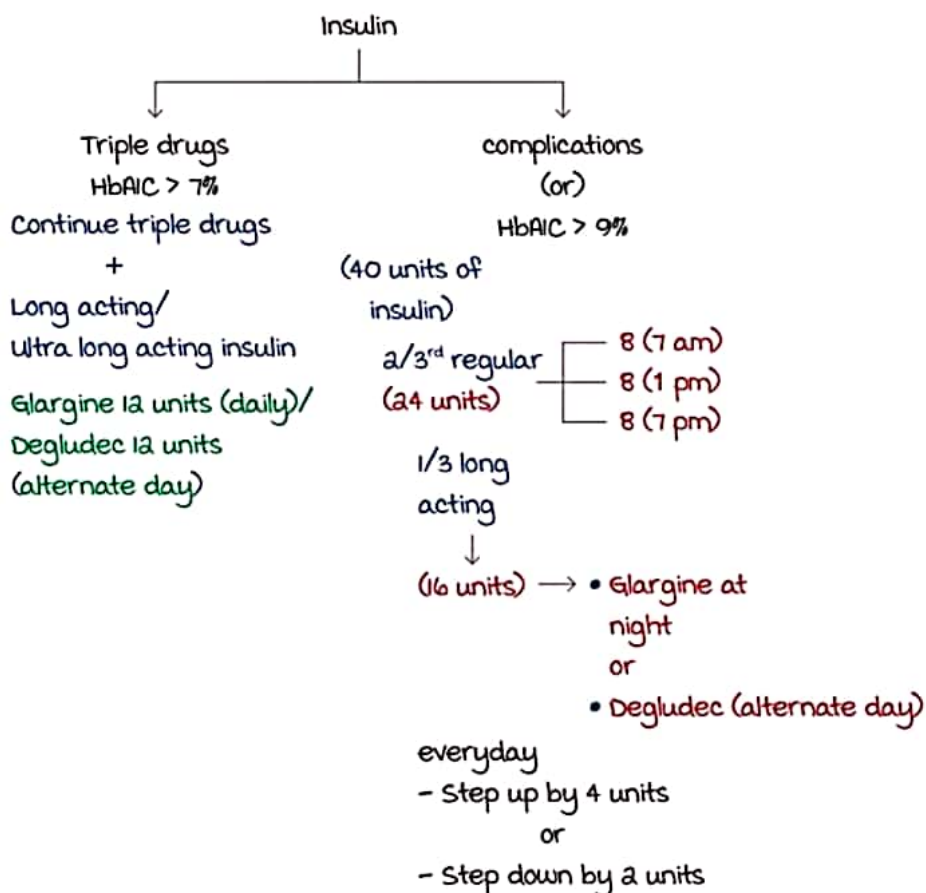


Insulin preparation

00:06:43

Type	Examples	onset of action	Peaks	Effective duration of action
ultra short Acting	Lispro, aspart, glulisine	<15 mins	1-1.5 hrs	4 hrs
Short acting	Regular	30 mins	1-3 hrs	3-6 hrs
Intermediate	NPH	2-4 hrs	4-10 hrs	10-14 hrs
Long	Glargine (acidic-can't be mixed)	1 hr	peakless	24hrs
	Detemir	2-3 hrs		
ultra long acting	Deqludec	2-3 hrs	peakless	> 40 hrs

- limitations of glargine - mitogenic risk ? Ca. thyroid weight gain
- Inter-individual variation



HYPOGLYCEMIA

- RBS < 70 mg/dl
- confusion or altered level of sensorium or seizure rule out Hypoglycemia
- Whipple's Triad
Clinically relevant hypoglycemia is characterized by:
 - 1) Characteristic neuroglycopenic symptoms
 - 2) Low Blood Glucose concentration (≤ 70 mg/dl)
 - 3) Resolution of symptoms with return of blood glucose concentration to $\textcircled{N}$

Symptoms:

Autonomic

- Sweating
- Trembling
- Pounding heart
- Hunger
- Anxiety

Neurologic

- Confusion
- Drowsiness
- Speech difficulty
- Inability to concentrate
- Incoordination

Non Specific

- Nausea
- Tiredness
- Headache

Physiologic responses to decreasing plasma glucose concentration

00:02:41

80-85 mg/dl	Insulin Falls	First defense
65-70 mg/dl	$\uparrow$ Glucagon	Second defense
65-70 mg/dl	$\uparrow$ Epinephrine	Third defense (critical when glucagon is deficient)
65-70 mg/dl	$\uparrow$ Cortisol and Growth hormone	Incase of prolonged hypoglycemia
50-55 mg/dl	symptoms	Prompt behavioral defense (Food ingestion)
<50 mg/dl	$\downarrow$ cognition	Comprises behavioral defense

Active space

- Hepatic glycogen stores are enough to maintain glucose levels for 8hrs only
- Brain requires glucose but, cannot Synthesize / utilize fatty acids
- In prolonged hypoglycemia, there is activation of cortisol and GH
- Dynamic thresholds – Higher than normal to be maintained in diabetic population
- CNS Glucose deprivation + sympathoadrenal discharge + Ach release (sweating)
- Increase platelet aggregation and inhibit fibrinolysis

Hypoglycemia in diabetics

00:07:00

- Drug induced – Insulin
Sulfonylurea
- CKD – Prolonged $t_{1/2}$ of insulin
↓ Renal Gluconeogenesis

Hypoglycemia associated autonomic failure (HAAF)

- Reversible entity

Early T₂DM:

(Relative β cell failure)



marked absolute

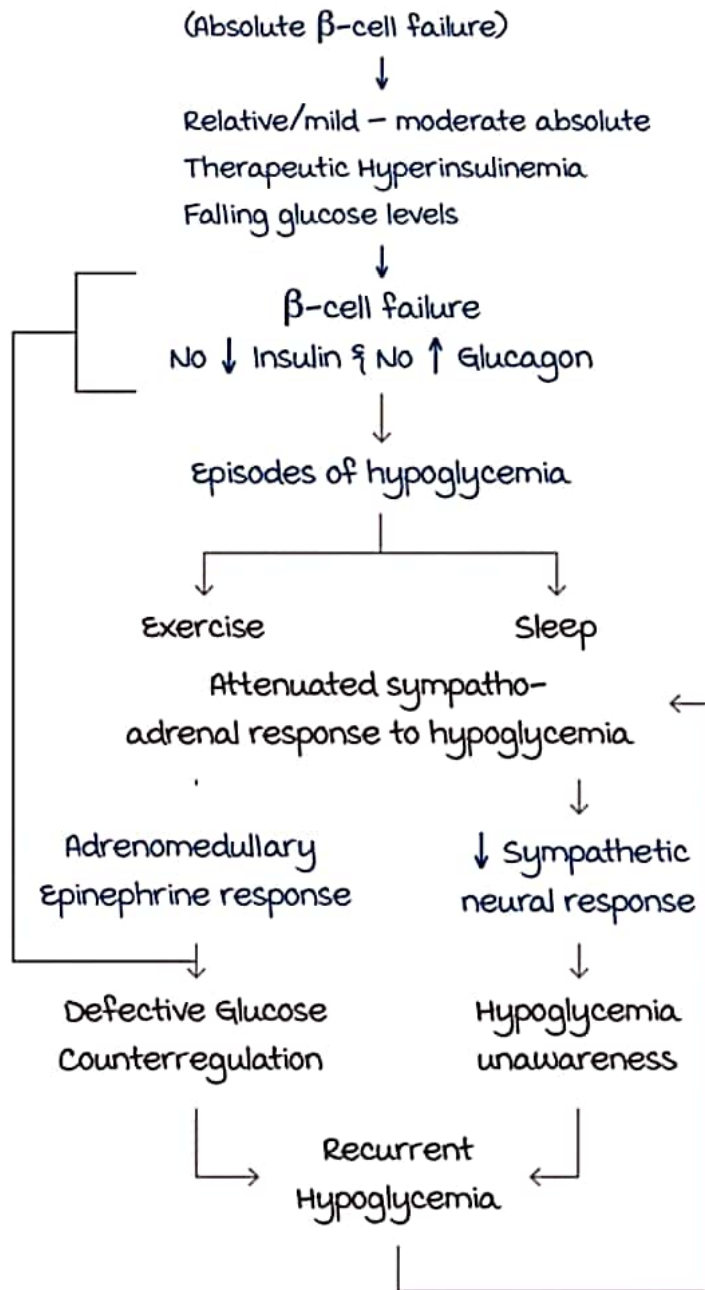
Therapeutic – Hyperinsulinemia



Falling glucose level



Isolated episodes of Hypoglycemia



Hypoglycemia without DM

00:12:30

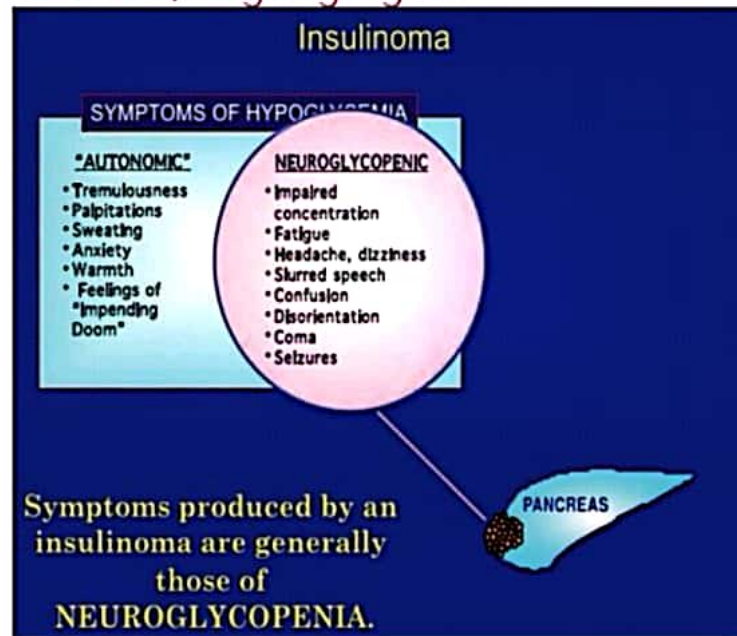
- Drugs - Ethanol
Beta Blockers
- Critical illness / Sepsis
- Addisons / GH deficiency
- Non - islet cell tumor dependent hypoglycemia in mesenchymal tumors - increased IGFa
- β-cell hypertrophy - **Nesidioblastosis**

Active space

- Insulinoma
- Antibodies to insulin receptor
- β -cell secretagogues [sulfonylurea, meglitinide]

⇒ plasma insulin $> 3 \mu\text{U/ml}$
 plasma C-peptide $> 0.6 \text{ ng/ml}$
 RBS $< 55 \text{ mg/dl}$
 plasma pro insulin $> 5 \text{ pmol/l}$

→ check for β - hydroxybutyrate



Hirata's disease (IAS)

00:15:57

- Insulin Autoimmune syndrome
- Antibodies against insulin
- > 40 Post prandial hypoglycemia
- Autoimmune association
- precipitated by methimazole
- Insulin molecule dissociates quickly causing marked hypoglycemia
- Spontaneous recovery in 80%

Hiratas disease v/s insulinoma

D Insulin / C-peptide ratio $< 1 \rightarrow \textcircled{N}$

If Insulin / C-Peptide ratio > 1

Either C-peptide low

or

Insulin $\uparrow\uparrow\uparrow$

Insulin $\uparrow\uparrow$

C-peptide $\uparrow$

[Exogenous insulin]

[Hiratas disease]

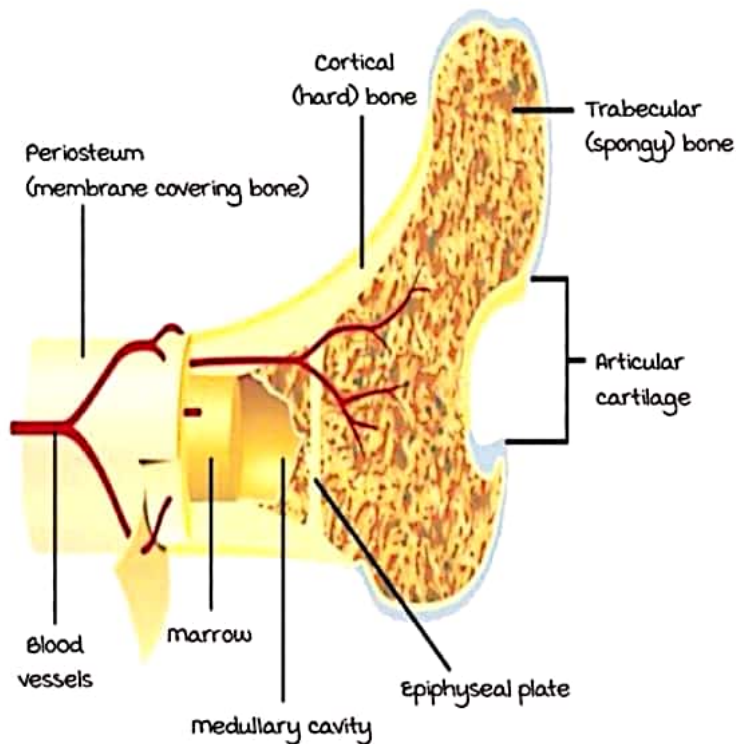
Treatment of Hypoglycemia

00:20:04

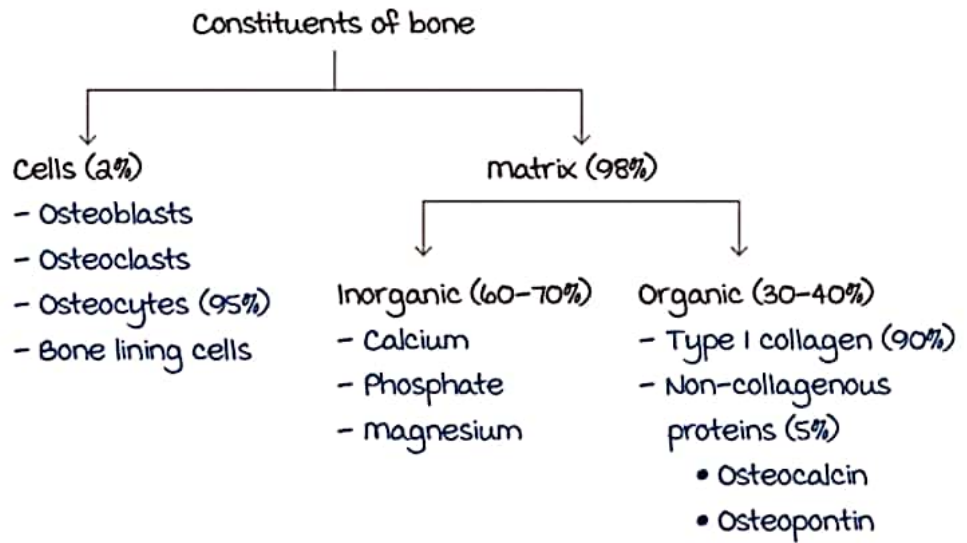
- Rule of 15 $\rightarrow$ 15g oral glucose & Check after 15mins
- symptomatic cases $\rightarrow$ 100ml of 25% dextrose - repeat
- If no I.V access give Im or S/C Glucagon 1mg

BONE AND MINERAL METABOLISM

- **Cortical bone (80%)** – bony cylinders arranged around central Haversian canal – diaphysis
- **20% trabecular bone** – more BMD / turnover
- Bone cells (2%) organic matrix (25%) mineral phase (75%)
- 95% of organic matrix is type 1 collagen
- Skeleton is highly vascular – **10% of total CO is to bones**



Parameters	Cortical	Trabecular
Synonyms	Compact bone	Cancellous, spongy
Contribution to total bone mass	80%	20%
Predominant sites	shaft of long bones	end of long bones, vertebra
Porosity	5-15%	30-90%
Haversian system	Present	Absent
metabolic activity	Low	High
Remodelling rate	Low	High
Predominant hormonal control	PTH, thyroxine	Gonadal steroids, glucocorticoids



Common (non-collagenous constituents)

- Osteopontin
- osteocalcin
- Thrombospondin
- matrix GLA protein
- Fibronectin
- Proteoglycans

Collagen

00:06:47

TYPE	SEEN IN
Type I	Bone
Type II	Cartilage, vitreous humor
Type III	Extensible connective tissue (skin + vascular)
Type IV	Basement membrane
Type V	Type I
Type VI	Non-specific
Type VII	Non-specific
Type VIII	Endothelium

Gene or enzyme	Disease
COL 1A1, COL1A2	Osteogenesis imperfecta, type 1 (MIM 156620) osteoporosis* (MIM 166710) Ehlers – Danlos syndrome type VII autosomal dominant (130060)
COL2A1	Severe chondrodysplasias osteoarthritis* (MIM 120140)
COL3A1	Ehlers – Danlos syndrome type IV (MIM 130050)
COL4A3 – COL4A6	Alport syndrome (including both autosomal and X- linked forms) (MIM 104200)
COL7A1	Epidermolysis bullosa, dystrophic (MIM 13750)
COL10A1	Schmid metaphysial chondrodysplasia (MIM 156500)
Lysyl hydroxylase	Ehlers – Danlos syndrome type VI (MIM 225400)
Procollagen N- Pro- α 1(I) procollagen	Ehlers – Danlos syndrome type VII autosomal recessive (MIM 225410)
Lysyl hydroxylase	Menkes disease (MIM 309400)

Mineralization

Amorphous CaPO_4
↓
Calcium hydroxyapatite
(on the matrix vesicles
on the metaphyseal end)

Enzymes inside vesicle

- ALP
- Annexins
- 5' nucleotidase

- Functional unit of a cortical / compact bone is called osteon
- Functional unit of spongy / cancellous bone : trabeculae
- Cancellous bone has increased surface area to mass ratio and hence responsible for 80% of total bone turnover
- Cancellous bone shows increased BMD while being treated for

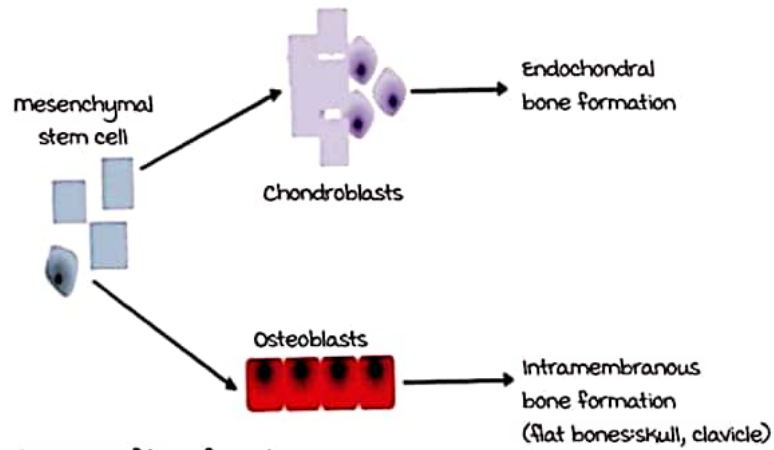
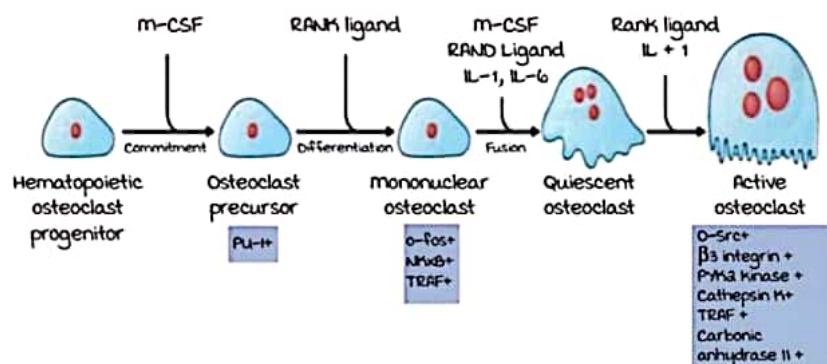
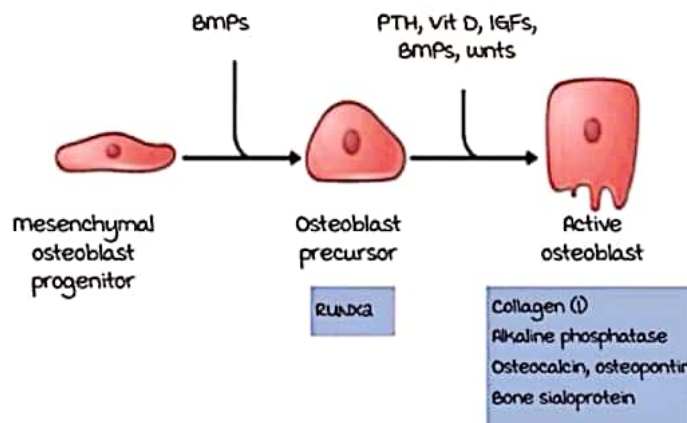


Fig: Types of bone formation

Osteoblasts

00:12:19

- mesenchymal origin
- Secretes organic matrix which is further mineralized and then cell becomes an osteocyte (mature)
- Osteocytes secrete **FGF-23**, mechanoreceptor function
- Transcription factor – **Runx2**



- **Osteocytes** are the master regulators of bone formation & resorption
- **FGF - 23** (Phosphaturic) inhibits 1α hydroxylase (in kidneys)
- Alkaline phosphatase is a marker for bone formation

Ligand independent activation of receptor (PTH / PTH-rp) $\rightarrow$ **Jansen's disease** (metaphyseal chondro dystrophy)

FGFR -3 $\rightarrow$ **Achondroplasia**

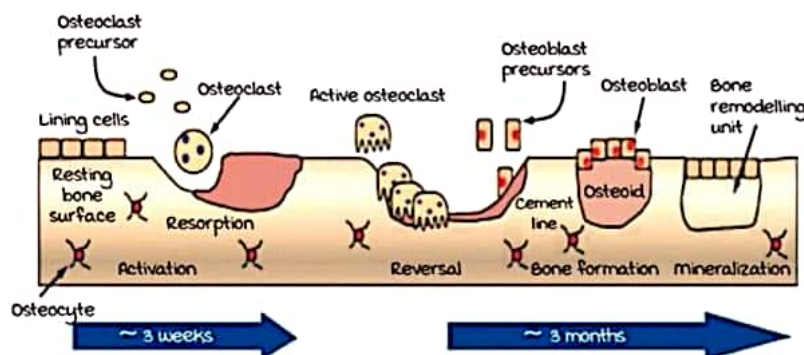
Carbonic anhydrase $\rightarrow$ **Osteopetrosis**

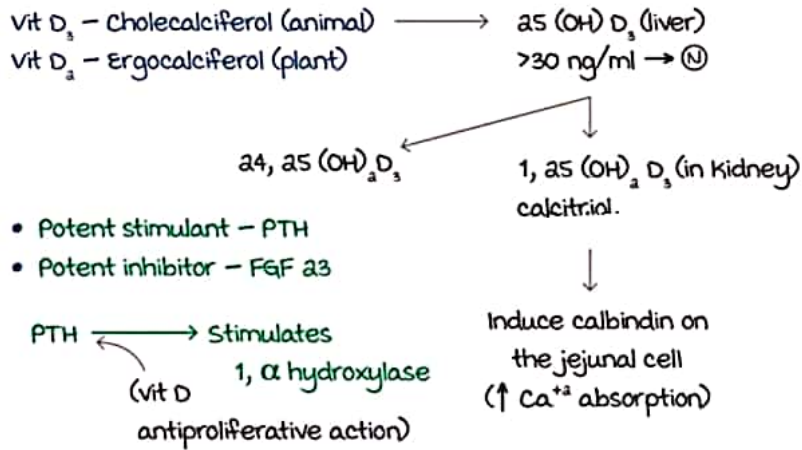
RANK ligand is produced by osteoblasts which recruits osteoclasts & **sclerostin** is produced by osteoblasts which prevents osteoclastogenesis

Osteoclasts

00:19:00

- Derived from macrophage
 - RANK ligand is produced by osteoblasts and binds to RANK receptor on the **surface of osteoclast progenitor**
 - PTH + Vit.D increase RANK ligand production from osteoblasts thus **increase** bone resorption
 - **Calcitonin** binds to receptor on basal surface of osteoclasts and thus inhibits action
 - Calcitonin causes hypocalcemia by stimulation of renal calcium clearance
 - Estradiol decreases osteoclast number inhibiting bone resorption
 - Irregular cavity formed by osteoclast resorption: Howships lacunae
 - Activation of osteoclast/ Resorption / Formation / Reversal / mineralization
- Stages $\rightarrow$ I II IV III V**
- Osteocytes regulate osteoblast by producing potent inhibitor of WNT pathway called **sclerostin**

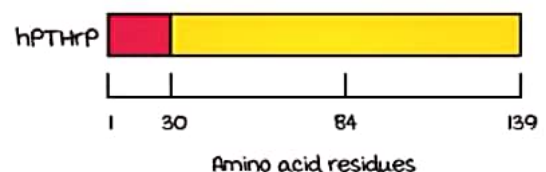
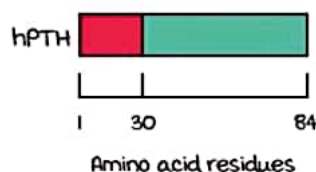




- osteocalcin and osteopontin → induced by vit D

	PTH	Vitamin D
Intestine	↑ Ca ⁺² and ↑ PO ₄ ⁺ absorption (by increased 1,25(OH) ₂ D production)	Increased calcium and PO ₄ absorption by 1,25 (OH) ₂ D
Kidney	↓ Ca ⁺² excretion ↑ PO ₄ ⁺ excretion	Ca ⁺² and PO ₄ excretion may be decreased by 25 (OH) D and 1,25 (OH) ₂ D
Bone	Ca ⁺² and PO ₄ ⁺ resorption increased by high dose, low doses may increase bone formation	↑ Ca ⁺² and PO ₄ resorption by 1, 25(OH) ₂ D; bone formation may be increased by 24, 25 (OH) ₂ D
No effect on serum	Serum calcium increase, serum phosphate decreased	Serum calcium and phosphate both increased

Active space



PTH :

- Intermittent PTH in low dose increases bone formation
- continuous PTH increase bone resorption
- Estrogen kills osteoclasts / 15-20% of bone mass is lost following menopause
- Senile osteoporosis – shift of mesenchymal stromal cells from osteoblast to adipocyte
- RANK ligand – RANK interaction is required for osteoclast differentiation
- Increase flow of calcium from bone to blood (PTH)
- Reduces renal clearance of calcium, increase Ca^{+2} reabsorption in DCT
- Induces 1 – α hydroxylase in PCT
- Inhibits phosphorus reabsorption at PCT
- Serum calcium is the most important regulator of PTH and deficiency of phosphorus impairs PTH release
- Loss of function mutation of CaSR produces familial hypocalciuric hypercalcemia
- Double antibody immunometric assays (estimation of intact PTH)

Markers of bone formation & resorption

00:43:59

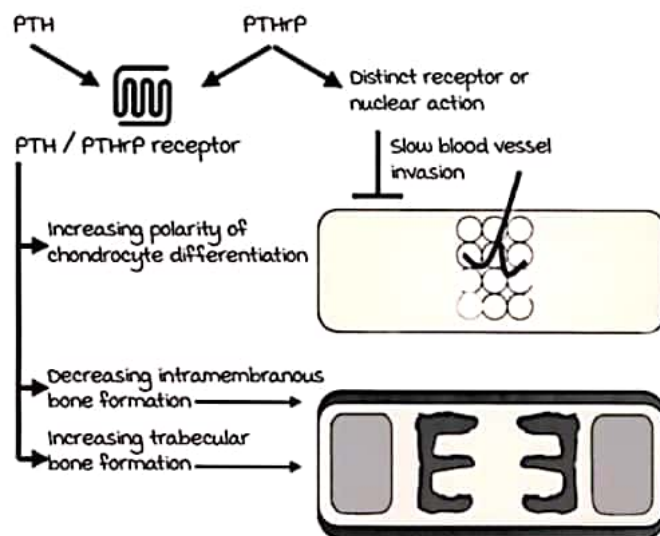
- Osteopontin / Fibronectin / Thrombospondin
- Osteonectin
- Osteocalcin
- ALP
- Procollagen peptide

markers of bone resorption

- TRAP (Tartarate Resistant Acid Phosphatase)
- Free deoxy pyridinoline in serum and urine
- Type I collagen N and C – Telopeptide breakdown products in serum and urine

Difference between PTH and PTHrP

00:45:18



- Enchondral ossification
- ↑ trabecular bone formation
- Ligand independent activation - Jansen's disease

Decrease in alkaline phosphatase

- malnutrition
- Zn/mg deficiency
- milk alkali syndrome
- Celiac disease
- Hypothyroidism

CALCIUM METABOLISM – I

- Body stores of calcium → 1 g – 1.3 g
 - 99.3% in bone
 - 0.6% in soft tissue
 - 0.1% in ECF
 - Daily diet has 1 g of calcium of which 20% is absorbed (200 mg)
 - 24 hours urinary Ca^{2+} → 4 mg/kg
 - 1st response to ↑ in Ca^{2+} → (calcium sensing receptor) in parathyroid
 - Sustained ↑ Ca^{2+} sensed by → CaSR in kidney
(Normal response → ↑ Ca^{2+} in blood → ↑ Ca^{2+} in urine)
 - Familial Hypocalciuric Hypercalcemia (FHH):
 - CaSR in kidney is non functional so, ↑ Ca^{2+} in blood is not sensed → ↓ Ca^{2+} in urine
 - Blood levels → 8.6 to 10.3 mg/dl
(Free ionized form → 48%
Protein bound form → 40%)
- Adjusted total Ca^{2+} → Total Ca^{2+} + 0.8 (4-S. Albumin)

Calcium absorption in intestine

00:05:08

- Absorption by active transcellular pathway (95%)
passive pathway (5%)
- Active absorption by TRPV_5 & TRPV_6 in jejunum which is tightly regulated by $1,25(\text{OH})_2\text{D}_3$ via calbindin
- Passive absorption is not tightly regulated, so if Ca intake > 4g/d, Ca^{2+} will enter system → milk alkali syndrome
- milk alkali syndrome → Hypercalcemia + hypercalciuria

Calcium in kidney:

00:07:34

- 60% passive reabsorption at proximal tubule
- 20-25% via paracellular pathway at thick ascending limb of Henle (through paracellulin (or) claudin)
- 10% in DCT via active transport (through TRPV_5 & TRPV_6)

- Patient no. I → 60 yrs old male, generalized tiredness, malaise, fatigue, weight loss, muscle weakness, bone pain (S. Ca^{2+} → 13 mg/dl)
- Patient no. II → 50 yrs old female, Recurrent episodes of UTI, with stones
- Patient no. III → 25 yrs old male with acute abdomen (pancreatitis), constipation, vomiting
- Patient no. IV → Referred from psychiatry department with psychiatric symptoms

Hypercalcemia (adjusted total S. Ca^{2+} >10.4 mg/dl)

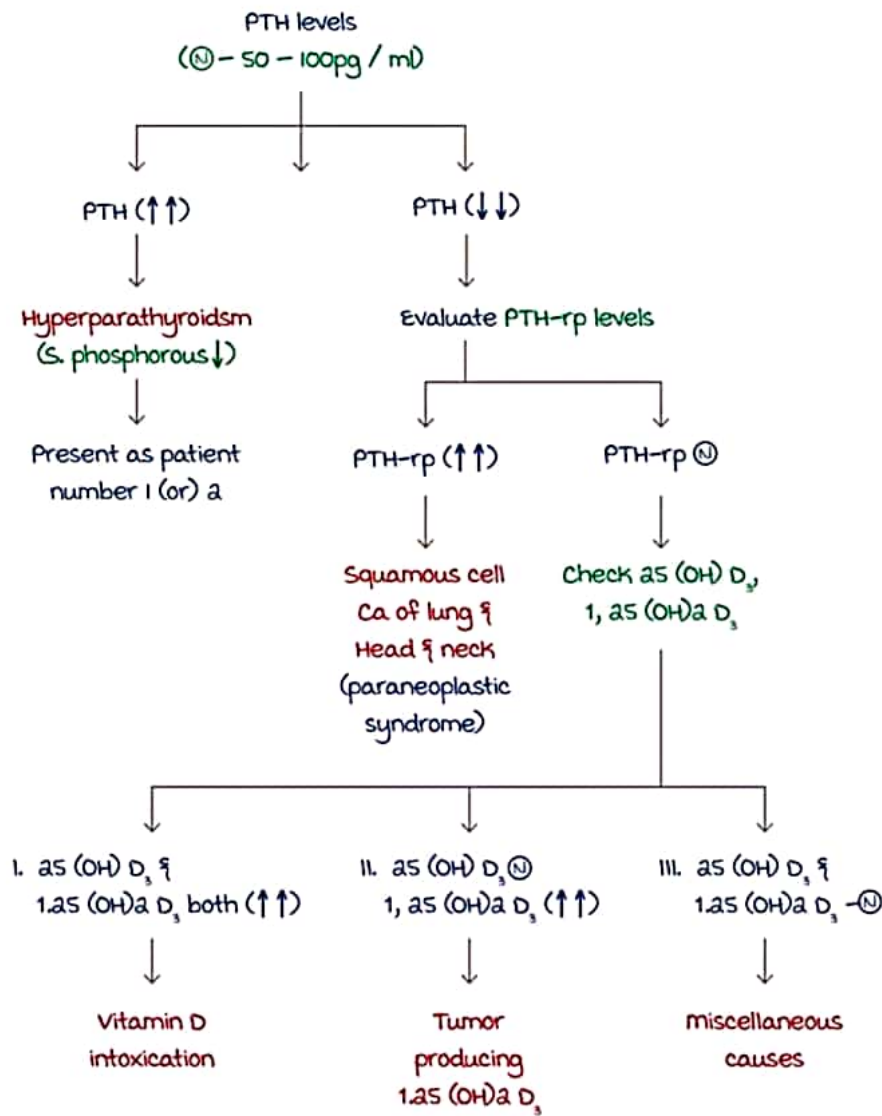


Confirm Hypercalciuria (>4 mg / kg) (↑↑)

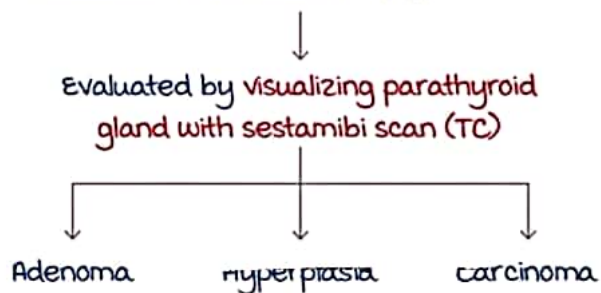
(Only exception → FHH)

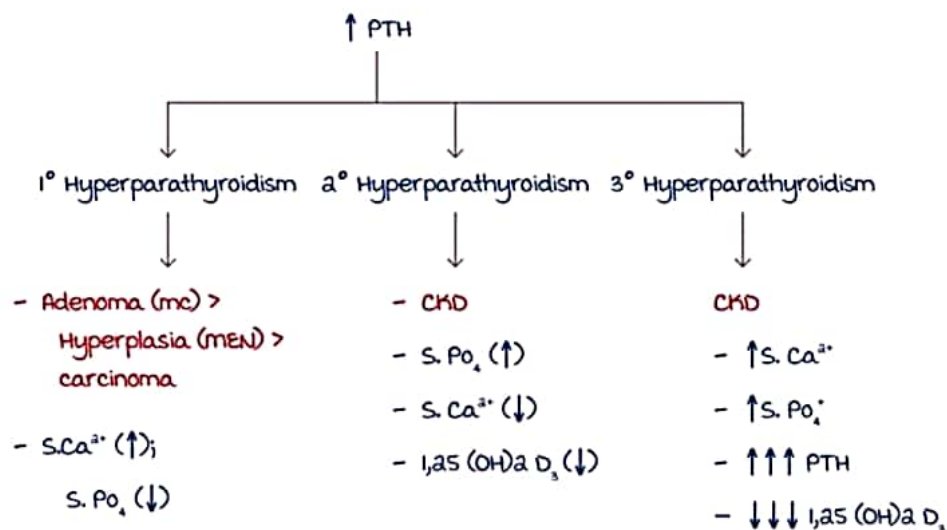


Check PTH levels iPTH (intact PTH)



- Patient no. 1 & 2 have PTH (↑↑)





X-ray findings in 1° hyperparathyroidism:

00:24:50

1) Bone resorption

- Diffuse
- mostly seen on Radial side of index and middle finger (proximal & middle phalanx)



2) Acral osteolysis (Tufting of phalanx)



3) Osteitis fibrosa cystica (Amorphous Ca²⁺ Phosphate)

4) Brown tumour

- Radiolytic areas where pseudotumour made of macrophages, blood & connective tissue



5) Rugger jersey spine



6) Intracortical bone resorption (Diffuse)

7) Endosteal bone resorption

8) subperiosteal bone resorption

9) skull

- Trabecular bone resorption
- Salt and pepper skull
- Pepper pot skull

Endosteal bone resorption

Endosteal scalloping



Management

00:29:56

I. Symptomatic → Surgery (removal of adenoma)

(If B/L Hyperplasia → near total parathyroidectomy)

II. Indications for surgery in asymptomatic individual ;

1. S. $\text{Ca}^{2+} > 1\text{mg/dl}$ from baseline

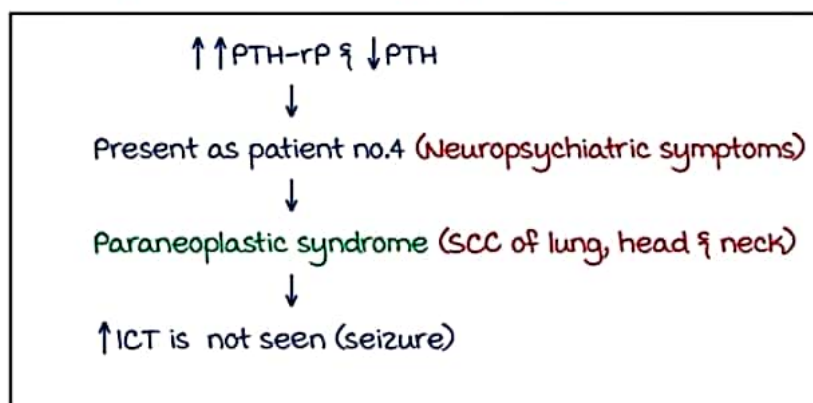
2. $\text{GFR} < 60 \text{ ml/min}$

3. ↓ Bone density

4. Age < 50 yrs

- 24 hour urinary Ca^{2+} is not an indication for surgery

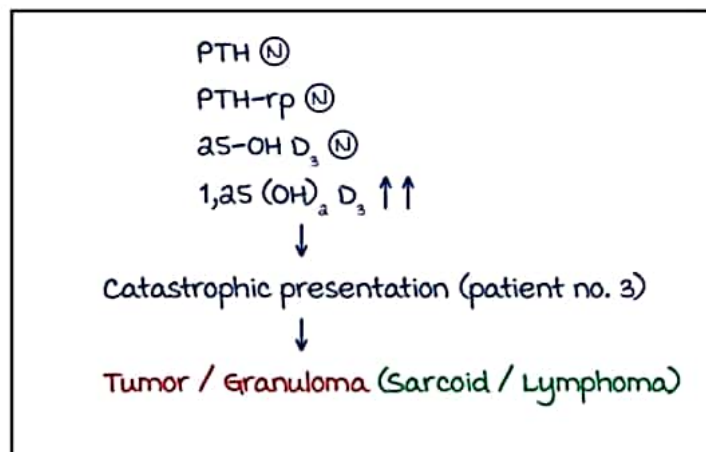
- No drugs are used for 1° Hyperparathyroidism



- Humoral hypercalcemia of malignancy
(due to ↑ PTH-rp) (low $1,25(\text{OH})_2\text{D}_3$)

SCC of lung / head / neck / cervix

- Treatment → management of primary cause
- Osteolysis in **multiple myeloma** can also cause hypercalcemia for which **steroids** may benefit



- Steroids are also useful in vit D related hypercalcemia

Miscellaneous causes:

00:36:56

1. Pheochromocytoma
2. Addison's disease
3. Acromegaly
4. Hyperthyroidism
5. Drugs → Thiazides

Lithium

Bones, Stones, Abdominal groans, Psychiatric moans

- Other symptoms;
 1. Nephrogenic DI symptoms
 2. **bradyarrhythmia** (short QT interval)
 3. muscle weakness (Hyperreflexia)
 4. **Band keratopathy**

PTH stimulates 1, α hydroxylase
PTH-rp inhibits 1, α hydroxylase

FHH:

- $\uparrow$ Ca^{2+} in blood; $\downarrow$ Ca^{2+} in urine
- Autosomal dominant
- Under 10 years
- Loss of CaSR in ThAC, DCT, Parathyroid gland
- Loss of CaSR only in kidney $\rightarrow$ mild hypercalcemia
- Very resistant to treatment

Hypercalcemic crisis:

00:41:56

- Characterised by severe dehydration, $\uparrow\uparrow$ S. Ca^{2+}
- Severe dehydration is due to Nephrogenic DI
- management $\rightarrow$
 - 1) IV fluids (500 ml/hr) then depending on output
(no role for Lasix)
 - 2) Calcitonin 4 units/kg stat if response given bd
 - 3) IV Bisphosphonate
 - Zolendronate 4 mg IV over 15min. (or)
 - Pamidronate 60 mg-90 mg IV over 2 hours
(starts to act in 1-2 days)
 - osteolysis in multiple myeloma or vit.D related crisis $\rightarrow$ glucocorticoids
 - No role for mithramycin & cliduminate
 - If nothing works $\rightarrow$ hemodialysis
 - Denosumab (monoclonal antibody against RANK can be tried)

CALCIUM METABOLISM – 2

Hypocalcemia

00:00:12

Hypocalcemia:

- S. Ca^{2+} : 8.6 to 10.3 mg/dl – (N)
- S. Ca^{2+} : ≤ 8.4 – hypocalcemia (8.5 considered as Borderline)
- S. Ca^{2+} : ≤ 7.4 mg/dl – severe hypocalcemia

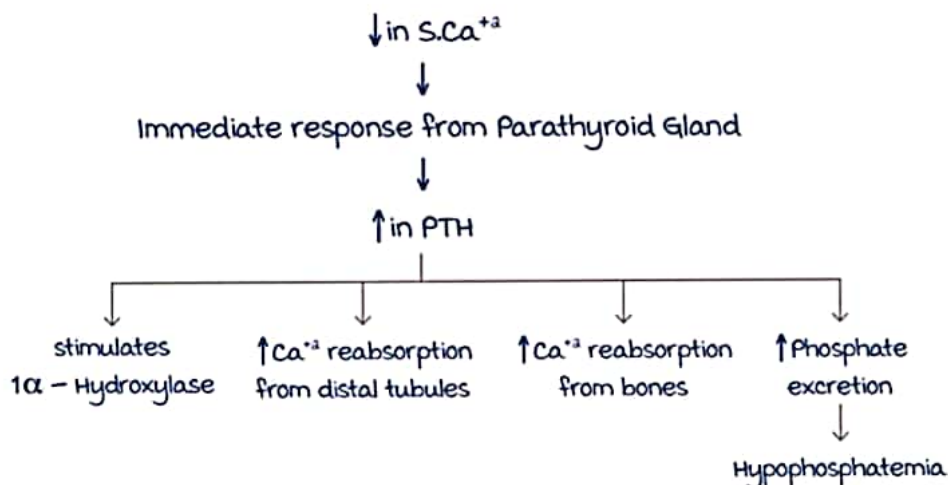
True adjusted Ca^{2+} = $\text{S.Ca}^{2+} + 0.8 (4 - \text{S. Alb})$

- 50% of this is ionised Ca^{2+}
- H^+ and Ca^{2+} is competing to bind with albumin
 - In acidosis – $\uparrow \text{H}^+$ Free ionised Ca^{2+} $\uparrow$
 - In alkalosis – $\downarrow \text{H}^+$ Free ionised Ca^{2+} $\downarrow$

- Symptoms of Hypo / hypercalcemia is due to increase / decrease in "ionised Ca^{2+} "

Acidosis = Hypercalcemia

Alkalosis = Hypocalcemia



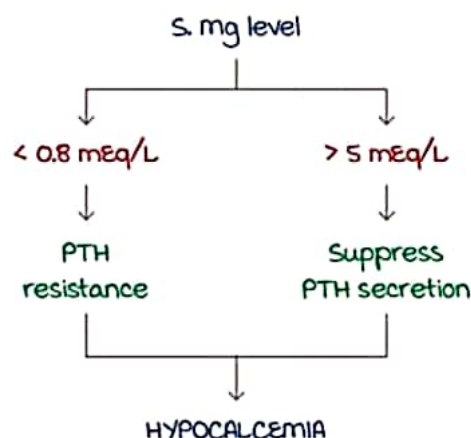
- Hypophosphatemia is due to inhibition of phosphate absorption → gets excreted more

Approach to hypocalcemia

00:07:33

Basic workup::

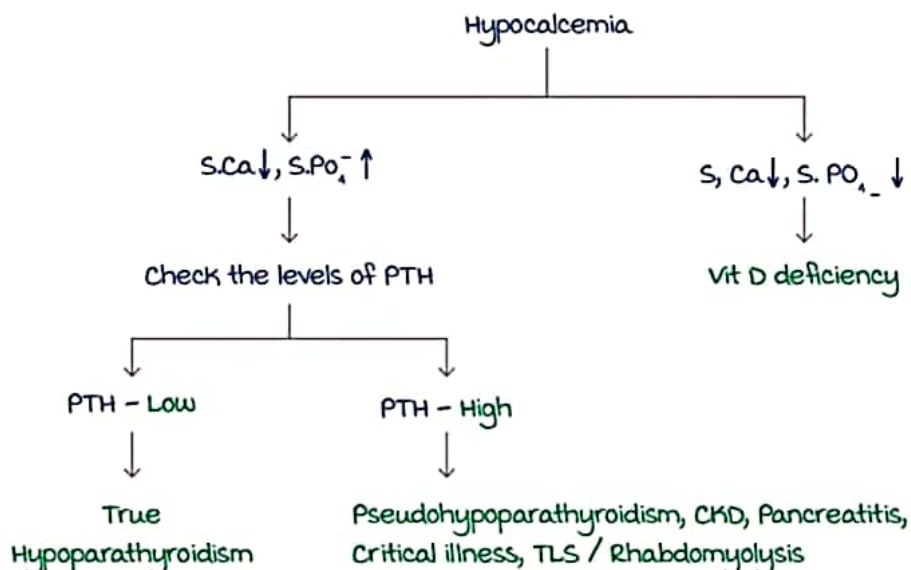
- Check for the levels of S. Alb, $\uparrow$ in H^+ or $\downarrow$ in H^+
- S. mg levels - normal - 1.5-1.9 meq/L



- Usage of drugs like cisplatin → Severe hypomagnesemia
- Infusion of large amounts of Citrate, (chelator) → , Hypocalcemia
- Plasmapheresis, massive blood transfusion can also lead to Hypocalcemia
- Antiviral drugs like Foscarnet → Produce more amount of citrate Hypocalcemia

Proper workup:

- Check the levels of S.phosphate



True hypoparathyroidism:

- MCC: 1. Surgical

- a. Transient hypocalcemia : due to prolonged Hypercalcemia prior to surgery
 - b. Hungry bone syndrome : due to prolonged decrease in S. Ca, S. PO_4 , S. Mg, loss of calcium Equilibrium
- Post surgery, bones take up the calcium, so $\downarrow$ in S. Calcium

2. Medical causes:

- a. Autoimmune: PGA Type 1 (Poly Glandular Autoimmune syndrome)
- b. Genetic: DiGeorge / CATCH 22 syndrome
 - microdeletions in 22q
 - C - cardiac Abnormalities - TOF
 - A - Abnormal Facies
 - T - Thymic Hypoplasia
 - C - Cleft Palate
 - H - Hypocalcemia
 - It is Autosomal dominant

CKD:

S. Ca^{2+} $\downarrow$, S. PO_4 $\uparrow$, S. PTH $\uparrow\uparrow\uparrow$



2° hyper parathyroidism in CKD,
It is due to increase in FGF-23



FGF-23 Inhibits 1α Hydroxylase



Decrease in calcitriol



↑ In PTH



↓ in Ca^{2+} absorption from intestine



Hypocalcemia



↑ In PTH

In CKD, after sometime FGF resistance occurs

↓
Decrease in number of nephrons

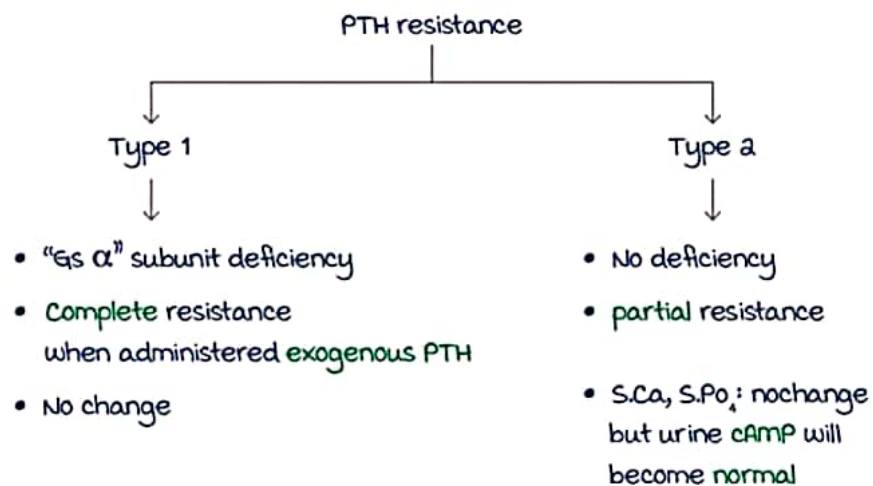
↓
Hyperphosphatemia

Disease	Cause	PTH	S.Ca	S.Po ₄
Primary Hyperparathyroidism	Adenoma	↑	↑	↓
Secondary Hyperparathyroidism	CKD	↑	↓	↑
Tertiary Hyperparathyroidism	Long Standing	↑↑	↑	↑

Pseudo hypoparathyroidism

00: 23:25

- It is characterized by PTH resistance



- Pseudo hypoparathyroidism:

a. Type 1a:

- Type 1a will have bone mineral changes
- It causes albright hereditary osteodystrophy
- Characterised by short stature, round facies, mental retardation, Short 4th metacarpal > metatarsal



b. Type 1b:

- Type 1b will not have any bone mineral changes

Pseudopseudohypoparathyroidism

00:27:03

- Pseudopseudohypoparathyroidism is just like PHP type 1a but biochemically it is normal (S.Ca²⁺, S.PO₄, S.PTH will be normal in pseudopseudohypothyroidism)

Type	Hypocalcemia hypophosphatemia	Response of urinary camp to pth	S.PTH	Gs α subunit deficiency	AHO	Resistance to hormones other than pth
PHP1A	YES	DECREASED	↑	YES	YES	YES
PPHP	NO	NORMAL	NORMAL	YES	YES	NO
PHP1B	YES	DECREASED	↑	NO	NO	YES
PHPa	YES	NORMAL	↑	NO	NO	NO

PHP = Pseudohypoparathyroidism PPHP = Pseudopseudohypoparathyroidism

Vitamin D deficiency

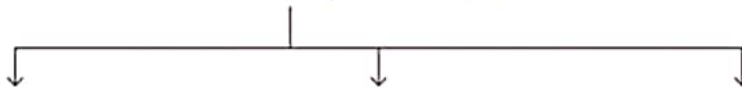
00:30:35

- S. Ca & S. PO₄ - Both are ↓

S. Ca, S. PO₄ ↓



Check for 25 (OH) D₃ & 1,25 (OH)₂ D₃



Drugs causing hypocalcemia

Drugs	mechanism causing hypocalcemia
1. Citrate, Foscarnet	Chelators of calcium
2. Bisphosphonates	
3. Cisplatin	Hypomagnesemia
4. Aminoglycosides, Amphotericin B	Tubular wasting

Symptomatology of hypocalcemia

00:34:29

Symptoms of acute hypocalcemia:

- Symptoms of acute hypocalcemia is characterized by neuromuscular symptoms

Acute mild:

- Characterized by circumoral paresthesias, twitching, tingling of Hands & feet, carpopedal spasms

Acute severe:

- Characterized by laryngospasm or seizure

Latent tetany:

- Characterized by Trousseau sign & Chvostek's sign
- Trousseau sign is also known as "main d' accoucheur"
- In severe hypocalcemia, there will be ↑QT interval leading to Torsades de pointes (polymorphic VT + prolonged QT interval)
- In severe hypocalcemia, there is ↑ICT, like pseudotumor cerebri leading to seizures & papilledema along with neuropsychiatric symptoms like irritability & depression

Symptoms of chronic hypocalcemia:

- Characterised by calcification
- Calcification commonly occurs in basal ganglia
- Dry skin, Brittle Hair
- Dental problems
- Cataract

Causes of chronic hypocalcemia:

- Genetic causes of hypoparathyroidism – DiGeorge
- Inherited syndromes with resistance to PTH – PHP
- Reversible impairment of PTH – like Mg^{2+} deficiency
- Acquired hypoparathyroidism – PGA type 1
- Vit D deficiency
- Vit D resistance – Type 2 VDDR
- Hyperphosphatemia / Tumor lysis
- Bisphosphonates
- Hungry bone syndrome
- Acute pancreatitis
- Drugs

Treatment of hypocalcemia

00:41:56

- In Acute severe or symptomatic or latent tetany
 - 1g (10ml) of Calcium gluconate 10% over 10 minutes, 1g contains 93mg of elemental calcium
 - 5g in 500ml 5% Dextrose at 1-3 mg of elemental calcium/kg/hr
 - Oral calcium upto 2g daily
 - Oral calcium contains CaCO_3 contains 40% elemental calcium
 - If the patient is stable, straight away treat with oral Ca^{+2} upto 2g/day
 - Vit D ($25(\text{OH})\text{D}_3$) if $< 30\text{ng/ml}$ is considered as deficiency and treated accordingly
 - Hypomagnesemia ($< 0.8\text{mg/l}$) $\Rightarrow$ I.V MgSO_4

PHOSPHORUS METABOLISM

- Body elemental stores of calcium = 1000 - 1300gm (99.3 in bone / 0.6 in soft tissue / 0.1 % distributed between tissue & ECF)
Phosphorus = 500 - 800 gm (85/14/1 %)

In bone : 99.3 % = calcium, 85% = phosphorus

- Phosphorus = • 2/3rd organic, 1/3rd inorganic
 - 50% ionised
 - 10 % is bound to albumin

Ⓝ serum level of phosphorus : 2.5 - 4.5 mg /dl

- 60 % absorption from intestine (regulated by vit. D)

• Phosphorus & Kidney :

- Excreted solely by kidney .
- In renal failure → Hyperphosphatemia
- Phosphorus reabsorption → Only at PCT (Na - P cotransporter)
Fibroblast growth factor - 23 = Inhibit Na - P_cotransporter

- Fractional excretion of phosphorus : - ↑ In proximal renal tubular acidosis (RTA)
- Ⓝ in Distal RTA

Hyperphosphatemia

00:04:50

- It is CKD - unless proved otherwise
- Other cause : Acute Kidney Injury, Tumor lysis syndrome, Rhabdomyolysis .
- In CKD → Phosphorus converts endothelial cells to osteoblasts



State of irreversible calcification ← trap calcium

- In CKD → maintain phosphorus levels < 5.5 mg /dl

Causes : i) ↑ Phosphorous intake : phosphate enemas for colonoscopy .

ii) ↓ Phosphorus excretion : CKD, AKI, Familial tumoral Calcinosis, Acromegaly

iii) Redistribution from : Cell to blood - • Tumor lysis syndrome
• Rhabdomyolysis
• Hemolysis
• Acidosis

Familial tumoral calcinosis

00:09:16

- AR
- due to missense mutation of $FGF\ 23 \rightarrow$ loss of function of $FGF\ 23$
- $\uparrow$ activity of $Na - P$ cotransporter = $\uparrow$ Phosphorus reabsorption
- This leads to calcium trapping $\rightarrow Ca_3(PO_4)_2$ deposition (bone / soft tissue)
- Symptoms due to :
 - Hypocalcemia
 - Calcification (vascular / soft tissue)



Fig. 13.7 (a, b) Plain radiograph of the hip (a) and hand (b) showing large calcified lesions involving upper thigh, distal femur, and palm suggestive of tumoral calcinosis

Hyperphosphatemia- clinical features & management

00:11:24

- Features :
 - Formation of widespread $CaPO_4$ precipitates
 - Tetany / seizures due to hypocalcemia
 - Pulmonary / cardiac calcification

Treatment : • Dialysis (if CKD)

- In other conditions - Treat hypocalcemia
- Oral phosphate binders

Calcium based : Calcium acetate
 Pure phosphate : Sevelamer,
 Lanthanum

Hypophosphatemia

00:12:54

- leads to Cardiomyopathy, Rhabdomyolysis, Hemolysis, Insulin resistance, Neuromuscular toxicity
- $\therefore$ To be addressed earliest

- To be symptomatic : Phosphorus levels $< 1\text{ mg/dl}$

- Cause :

- ↓ Phosphorus in diet
- ↑ excretion from kidney : Na - P cotransporter defect, PCT defect
- Cellular shift FGF- 23 gain of function mutation



Tumor induced Osteomalacia

- Hypophosphatemic rickets : - Na- p cotransporter defect
- X - linked or AD or AR



mc → Phosphate-regulating neutral endopeptidase X linked gene

- Proximal RTA : • Proximal tubular defect
- mc - Fanconi syndrome

- Transcellular shift → • Alkalosis
- Hungry bone syndrome
- Refeeding syndrome (Alcoholics)
- DKA after insulin therapy
- Sepsis

- Symptoms : Proximal myopathy, Bone pain, myocardial function impaired, Neurological symptom - Rare .

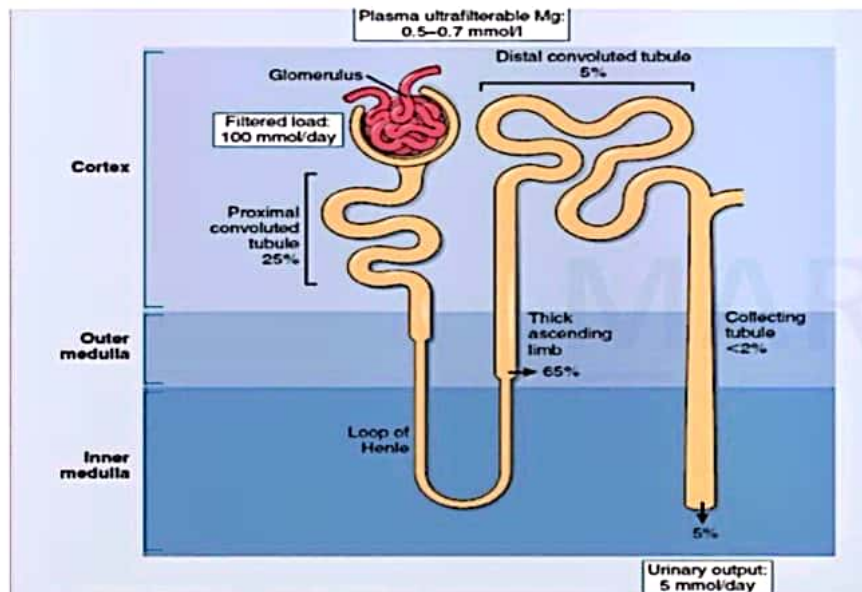
Treatment : Iv phosphorus replacement (if serum level is < 1 mg /dl)

Tumor induced osteomalacia :

- mesenchymal / Fibrogenic Tumor, lymphoma secreting FGF - 23 .
- Paraneoplastic condition
- Ca ²⁺ levels → (N)
- Phosphaturia (+)
- ↓ in bone mineralization

MAGNESIUM METABOLISM

- (N) level = 1.5 - 1.9 meq / litre
- 2nd most abundant intracellular cations (after potassium)
 $2 \text{ meq / l of } \text{Mg}^{2+} = 1 \text{ mmol / l of } \text{Mg}^{2+} = 2.4 \text{ mg / dl}$
- magnesium in kidney :



- All the ions in humans are maximally reabsorbed in PCT except Mg^{2+}
- Mg^{2+} reabsorption :
 - 25% at PCT - Passive transport
 - 65% at Thick Ascending limb of loop of Henle
 - Paracellular pathway
(via paracellulin / claudin)
 - 5 - 10% actively reabsorbed at DCT (by TRPM6)
 - Active transport

Hypermagnesemia

00:03:07

- Pediatric cause : • FHH (Familial Hypocalciuric Hypercalcemia)
- Symptoms ;
 - $\uparrow$ Serum $\text{Mg}^{2+} > 3 \text{ meq / litre}$ cause PTH impaired production
 - decrease in serum $\text{Mg}^{2+} < 0.8 \text{ meq / litre}$ cause PTH resistance
 - decrease in Serum Mg^{2+} impaired tubular secretion of K^+ $\rightarrow$ Refractory Hypokalemia
 - 4 - 6 meq / l - Nausea, flushing, headache, drowsiness, sluggish deep tendon reflex (DTR)

- $6 - 10 \text{ meq/l}$ - Hypocalcemia, $\downarrow$ DTR, Bradycardia, hypotension.
- $>10 \text{ meq/l}$ - Flaccid quadriplegia, respiratory failure, cardiac arrest
- $>12 \text{ meq/l}$ - Cardiac arrest $\rightarrow$ Block Ca^{2+} & K^{+} Channels



- PR - Prolongation
- QRS widening
- QT Prolongation (rare)

Diagnosis - CKD (unless proved otherwise)

Treatment - Dialysis

Hypomagnesemia

00:10:34

- I. Impaired intestinal absorption
 - A. Hypomagnesemia with secondary hypocalcemia (TRPM6 mutations)
 - B. Malabsorption syndromes
 - C. Vitamin D deficiency
 - D. Proton pump inhibitors
- II. Increased intestinal losses
 - A. Protracted vomiting/diarrhea
 - B. Intestinal drainage, fistulas
- III. Impaired renal tubular reabsorption
 - A. Genetic magnesium-wasting syndromes
 1. Gitelman's syndrome
 2. Bartter's syndrome
 3. Claudin 16 or 19 mutations
 4. Potassium channel mutations (Kv1.1, Kir4.1)
 5. $\text{Na}^{+}/\text{K}^{+}$ -ATPase γ -subunit mutations (FXD2)
 - B. Acquired renal disease
 1. Tubulointerstitial disease
 2. Postobstruction, ATN (diuretic phase)
 3. Renal transplantation
 - C. Drugs and toxins
 1. Ethanol
 2. Diuretics (loop, thiazide, osmotic)
 3. Cisplatin
 4. Pentamidine, foscarnet
 5. Cyclosporine
 6. Aminoglycosides, amphotericin B
 7. Cetuximab
 - D. Other
 1. Extracellular fluid volume expansion
 2. Hyperaldosteronism
 3. SIADH
 4. Diabetes mellitus
 5. Hypercalcemia
 6. Phosphate depletion
 7. Metabolic acidosis
 8. Hyperthyroidism

Causes :

- $\downarrow$ intake of Mg^{2+}
- Drugs :
 - PPI's
 - Cisplatin
 - Pentamidine
 - Cetuximab

- Aminoglycosides , Amphotericin B
- ↑ renal secretion of magnesium .
- 1) **Bartter's syndrome**
 - Hypermagnesuria with normal serum magnesium.
- 2) **Gitelman's syndrome**
 - Hypomagnesemia due to inhibition of TRPM 6 in the intestine .

Transcellular shift :

IV. Rapid shifts from extracellular fluid

A. Intracellular redistribution

1. Recovery from diabetic ketoacidosis
2. Refeeding syndrome
3. Correction of respiratory acidosis
4. Catecholamines

B. Accelerated bone formation

1. Post-parathyroidectomy
2. Treatment of vitamin D deficiency
3. Osteoblastic metastases

C. Other

1. Pancreatitis, burns, excessive sweating
2. Pregnancy (third trimester) and lactation

- Symptoms :
 - Neuromuscular hyperexcitability
- Tetany , muscle spasms & cramps
- Seizures
- Vertical nystagmus .
- Respiratory muscle involvement
 - (cardiac) inhibiting Na-K ATPase
- magnesium competes with Digoxin to bind with Na-K ATPase .
- Hypomagnesemia → ↑ Digoxin binding

↓
 Digoxin toxicity .
- Ventricular tachyarrhythmias .
- Widening of QRS
- ↑ QT
- Polymorphic VT .

-Hypocalcemia

- Hypoparathyroidism
- Decreased bone mass.

- Hypokalemia → ↑ tubular secretion of potassium

Management of hypomagnesemia

00:16:35

- Severe symptoms :

iv mgso₄ (2g) (16meq)



10% in 10 min

- Continue correction even after achieving normal blood level to correct intracellular depletion

- mild symptoms : magnesium oxide tablets

- Amiloride
- Triamterine

→ Associations

- myocardial infarction
- Hypokalemia
- Hypocalcemia
- Insulin resistance
- migraine
- Colon cancer

OSTEOPOROSIS

Osteoporosis

00:00:32

- Quantitative bone disorder .

- Decrease in

(1) Osteoid matrix

(2) mineral phase

(3) Bone mineral density or

(4) Peak bone mass .

“ micro architectural bone distortion ”

(Bone geometry is affected)



“ Pathological fractures ”

- Peak bone mass:

→ Spine : 20 years

→ Long bones : 25 - 30 years .

- Pathological fracture → vertebral (mc) > Hip > Distal radius .

- after 70 years → Hip fracture

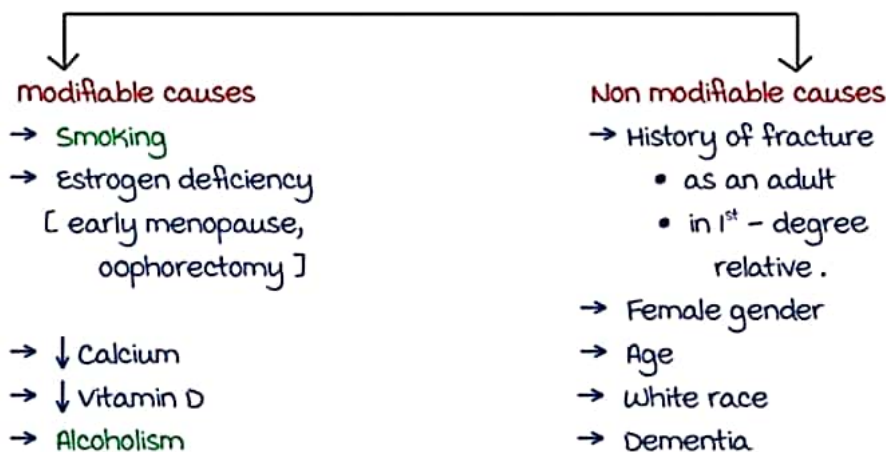
- Distal forearm fractures are the early & sensitive marker of bone fragility in males .

- mc in post menopausal females (40%)

- Secondary osteoporosis is due to metabolic causes

Risk Factors for osteoporosis

00:04:36



Secondary causes of osteoporosis :

→ **Drugs**

- (1) Steroids
- (2) Proton pump inhibitors .
- (3) Heparin
- (4) Lithium
- (5) SSRIs
- (6) Cyclosporine .
- (7) Pioglitazone .
- (8) Eltroxin

→ **Hypogonadism**

- Hyperprolactinemia
- Turner's syndrome
- Klinefelter's syndrome .

→ **Endocrine disorders .**

- Hyperparathyroidism
- Cushing's syndrome .
- Diabetes mellitus [Type I & 2]
- Thyrotoxicosis .
- Adrenal insufficiency . (Addison's)

→ **Rheumatological disorders :**

- Rheumatoid arthritis .
- Ankylosing spondylitis .

→ **Miscellaneous causes :**

- Multiple myeloma .
- Thalassemia
- Hemochromatosis .
- Marfan's syndrome .
- Ehlers - Danlos syndrome .
- Sarcoidosis . / Amyloidosis .
- Immobilization .

Pathophysiology :

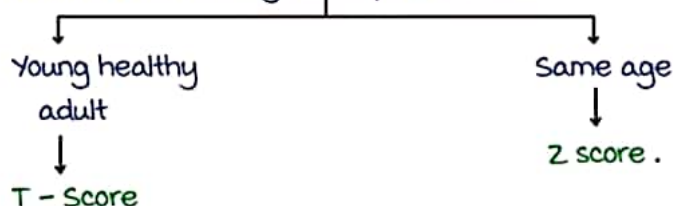
- (1) ↑ Peak bone mass
- (2) ↑ Osteoclastic activity
- (3) ↓ Osteoblastic activity .
- (4) Micro architectural bone changes .

- **Dexa - Scan** : [Dual energy x-ray absorptiometry]

→ Indications :

- Women > 65 years / men > 70 years .
- Younger males / females with risk factors .
- Prior fragility fracture
- Family history .
- Smoking
- Steroid
- Alcoholic
- Rheumatoid arthritis / Ankylosing spondylitis .

- Bone mineral density in comparison with :



- Score : 0 to -1 → normal
 - 1 to -2.5 → osteopenia
 - 2.5 & above → osteoporosis
- " T - Score -2.5 ~ Z - score -1 "

Treatment Of Osteoporosis

00:12:14

- Smoking cessation
- Physical activity
- Stop alcohol
- Adequate calcium - 1000 mg/ day .
- Vitamin D - 2000 IU/day .

Drugs

- (i) **Inhibitors** of bone resorption :

a) Bisphosphonates : [**DOC**]

- Alendronate
- Risedronate
- Ibandronate
- Zoledronate

Active space

- b) Calcitonin
- c) HRT
- d) SERM.

a) Stimulators of bone formation.

- Fluoride
- Recombinant PTH - Teriparatide

3) mixed mechanism

- Strontium ranelate

4) Adjunctive therapy

- Calcium
- Vitamin D

→ Denosumab - (antibody against Rank ligand)

Bisphosphonates, HRT & SERM

00:18:20

Bisphosphonates :

- Oral bisphosphonates (DOC)
- Drugs :

- Risedronate
- Alendronate - 70 mg once a week
- Ibandronate - 150 mg monthly
- IV - zoledronate - 5mg
- Very poor oral absorption - hence to be taken on empty stomach 30 minutes before the 1st meal & remain upright for 30 minutes.

→ Side effects :

- Jaw necrosis
- FSGS
(Pamidronate → Collapsing FSGS)
- Hypocalcemia.

HRT (hormone replacement therapy)

- Side effects :
 - (1) Breast cancer
 - (2) CHD
 - (3) Stroke

→ "Severe hot flushes" → Only indication for HRT.

SERM (Selective estrogen receptor modulator)

- **Tamoxifen**

- antagonist → Breast & blood vessels.
- agonist → Over all

Side effects :

- Cramps
- hot flushes
- ↑ risk for endometrial cancer.
- Thromboembolism.

- **Raloxifen.**

- antagonist on endometrium → No risk of endometrial cancer.
- SE : Thromboembolism.

Calcitonin And rPTH

00:21:50

Calcitonin

- Weak anti resorptive drug
- route : intranasal or subcutaneous.
- tachyphylaxis or rapid tolerance
- "No effect on non-vertebral fractures"
- Drug is given preferentially in older women with multiple fractures.

Recombinant PTH

- Drugs :

(1) Teriparatide

(2) Abaloparatide.

→ Intermittent PTH exposure



stimulates bone formation & decreases sclerostin

→ Chronic PTH exposure



↑ RANKL ; ↓ (OPG) Osteopontogenin (Physiological inhibitor of RANK - L)



Bone resorption



Osteoporosis

Route : Subcutaneous.

→ **Strontium Ranelate** :

- both resorptive and osteotrophic
- Side effects :
 - Diarrhoea
 - Thromboembolism
 - Seizures

→ monoclonal antibody against RANK - L

- Denosumab
- Romosozumab

Radiological abnormalities :

(i) **Codfish spine** or .

Fish mouth vertebrae

[Osteomalacia > Osteoporosis]

(a) **Dowager's hump**

Curvature of spine

(3) Wedge compression fractures

Surgical management :

→ vertebroplasty (Poly methyl methacrylate)

HYPOKALEMIA

Potassium metabolism

- major intracellular cation
- mostly in the muscle

$$1 \text{ mmol of } K^+ = 1 \text{ meq of } K^+ = 40 \text{ mg } K^+$$

Normal serum $K^+ = 3.5 - 5.5 \text{ meq/l or mmol/l}$

$$\begin{aligned}\text{Total body } K^+ &= 50 \text{ meq} \times \text{body weight} \\ &= 50 \text{ meq} \times 60 \\ &= 3000 \text{ meq}\end{aligned}$$

Conc. of K^+ in the cell = 145 to 150 meq/l

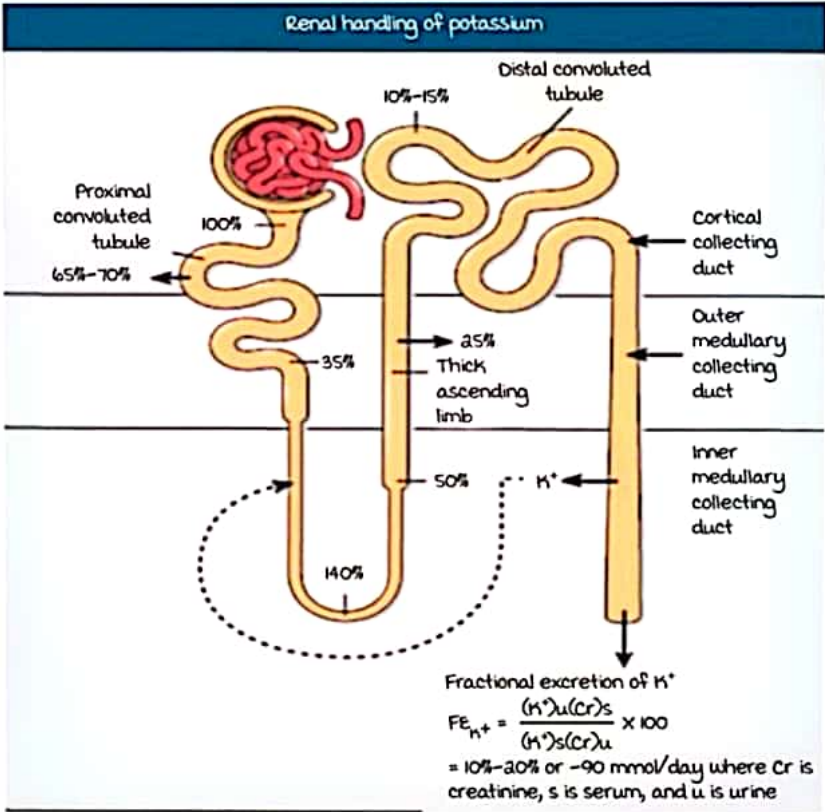
- The normal ratio between extracellular and intracellular concentrations is important for maintenance of resting membrane potential (RMP) and neuromuscular functioning
- Intracellularly, potassium is required for cell growth, maintenance of cell volume, DNA and protein synthesis, enzymatic function and acid-base balance

Distribution of Total Body Potassium in organs and Body compartments			
Organs and Compartments		Body Compartment Concentrations	
Muscle	2650 mmol	Intracellular Concentration	150 mmol/l
Liver	250 mmol	Extracellular Concentration	4 mmol/l
Interstitial fluid		35 mmol	
Red blood cells		35 mmol	
Plasma		15 mmol	

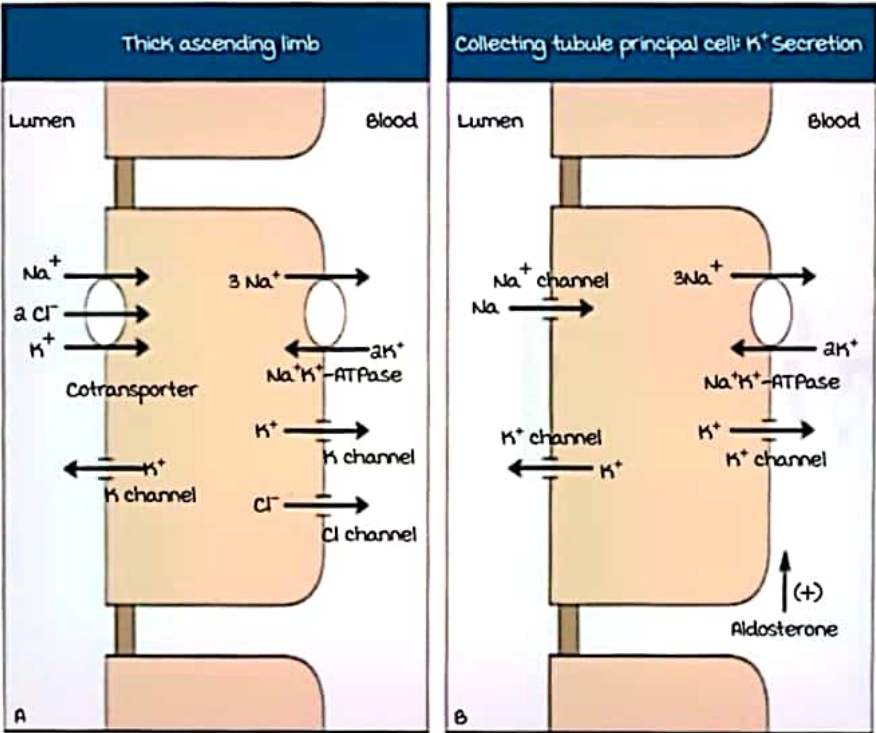
Renal handling

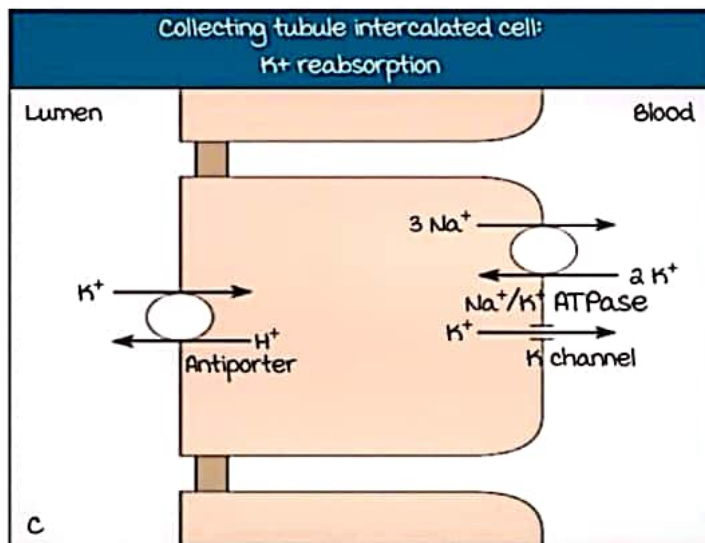
00:03:55

- 90% of K^+ - excreted by kidney



Active space





α - Integrated cell of cortical collecting duct (CCD)

Hypokalemia - clinical presentation

00:07:32

I muscle:

- muscle weakness / Paralysis
- Flaccid muscle paralysis
- No sensory involvement

II Cardiac - ECG changes / Arrhythmias

III Smooth muscles

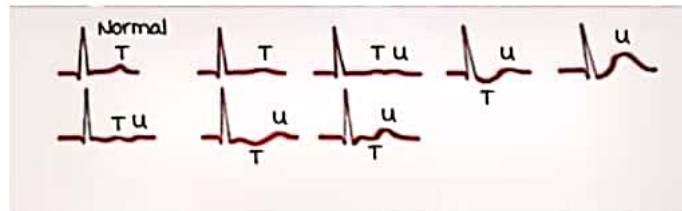
- Constipation
- Ileus
- Bladder dysfunction

IV Renal

- Nephrogenic diabetes insipidus (DI) $\rightarrow$ Polyuria
- Structural Damage to Kidney $\rightarrow$ Chronic Tubulointerstitial Disease (Dilation and vacuolization of PCT)

Miscellaneous

- $\uparrow$ Renal NH₄ Production
Hepatic Encephalopathy
- Decrease insulin secretion
Carbohydrate intolerance



The ECG patterns that may be seen with hypokalemia range from slight T wave flattening to the appearance of prominent u waves, sometimes with ST segment depressions or T wave inversions. These patterns are not directly related to the specific level of serum potassium

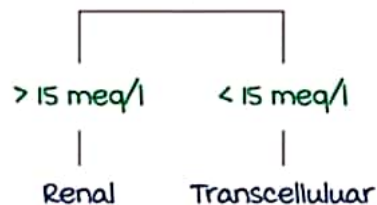
- Flat "T" wave
 - Prominent "u" wave
 - ST depression
 - QT prolongation
 - PR prolongation
 - wide QRS
 - ventricular arrhythmias
 - Decreased voltage
- 3.5-4 meq/l
 - 3-3.5 meq/l : flattening of 'T' wave
Prominent 'u' wave
Prolonged QT interval/QU interval
 - <3 meq/l : sagging /depression of ST segment
 - <2.5 meq/l : QRS widening
↑ risk of arrhythmia
PR Prolongation

Approach to patient with hypokalemia

00:15:10

1) Look for Renal (or) spot K^+

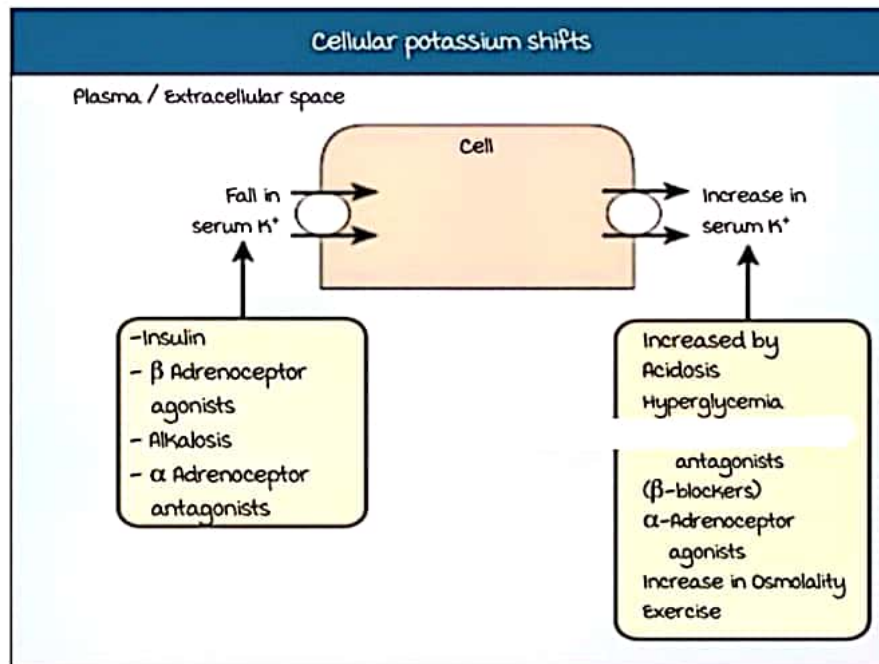
urine spot K^+



Causes of :

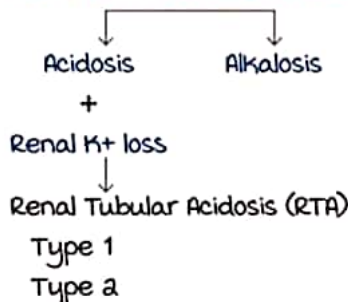
- Transcellular shift (From blood to cell)
 - Insulin
 - Salbutamol
 - α - Antagonist
 - metabolic alkalosis
- Transcellular shift (cell to blood)
 - β -blockers
 - α - Agonist
 - Acidosis

- Hyperglycemia
- Hyperosmolality
- Exercise
- ↑ Hormones (GH, Thyroid)



Renal causes for hypokalemia

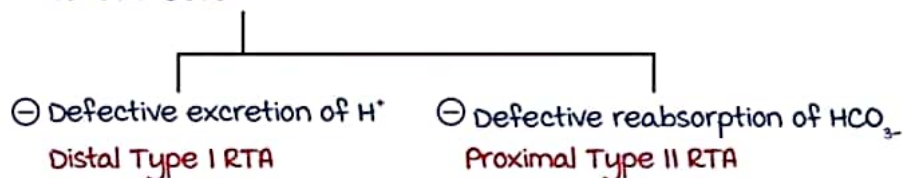
(ABG- Arterial Blood Gas)



Renal tubular acidosis

00:20:14

• Tubular Defect



- metabolic Acidosis
- Alkaline urine

RTA type I (Distal RTA)

1. Causes:

- Defect in α -intercalated cell of CCD (mainly)
- β -intercalated cells (rarely)
- 2. Defective H^+ ATPase or $H^+ K^+$ ATPase
- 3. Can be primary (majority) / secondary
- 4. Primary distal RTA seen in children (5-10yrs)
- 5. Never progresses to CKD
- 6. Metabolic Acidosis

+

Alkaline urine (pH > 5.5)

Severe metabolic acidosis

- $\uparrow Ca^{++}$ resorption from Bone



- Hypercalcemia
- Hypercalciuria → Stone Formation

- Hypocitraturia

- Volume depletion $\uparrow$



$\uparrow$ RAS (Renin angiotensin system)

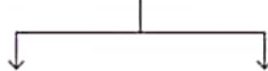
$\uparrow$ aldosterone



K^+ wasting → Hypokalemia

RTA Type II (Proximal RTA)

- Generalised proximal tubular dysfunction
- Less severe acidosis



Stone formation nil Less RAAS activity
less hypokalemia

Generalised proximal tubular dysfunction

- Glucose → Glycosuria
- amino acid → Aminoaciduria
- Bone mineral Changes
- Phosphorous wasting
- Rickets

Causes of hypokalemic distal (type I) RTA

Primary

- Idiopathic
- Familial

Secondary

- Autoimmune disorders
 Hypergammaglobulinemia
 (MCC of distal RTA)
 Primary biliary cirrhosis
 SLE

Genetic diseases :

- Autosomal dominant (AD)
defective anion exchanger
- Autosomal recessive (AR)
defective H⁺ ATPase

• Drugs and Toxins

Amphotericin B

Toluene

• Disorders with Nephrocalcinosis

Hyperparathyroidism

Vit D intoxication

Idiopathic hypercalciuria

• Tubulointerstitial disease (TID)

Obstructive uropathy

Renal transplantation

Causes of proximal (Type 2) Renal Tubular Acidosis	
Not associated with renal tubular dysfunction	
Sporadic	
Familial	
Disorder of carbonic anhydrase	
Drugs: acetazolamide, sulphanilamide, topiramate	
Carbonic anhydrase II deficiency	
Associated with Fanconi syndrome	
Selective (no systemic disease present)	
1. Sporadic	
2. Familial	
Autosomal recessive proximal RTA with ocular	
Abnormalities: Na ⁺ HCO ₃ ⁻ cotransporter (NBCe1) defect	
Autosomal recessive proximal RTA with osteopetrosis	
and cerebral calcification: carbonic anhydrase II defect	
Generalized (systemic disorder present)	
Genetic disorders	
Cystinosis	
Wilson's disease	
Hereditary fructose intolerance	
Lowe syndrome	
metachromatic leukodystrophy	
Dysproteinemic states	
myeloma kidney	
Light chain deposition disease	
Primary and secondary hyperparathyroidism	
Drugs and toxins	
Outdated tetracycline	
Ifosfamide	
Gentamicin	
Streptozocin	
Lead	
Cadmium	
Mercury	
Tubulointerstitial disease	
Post transplantation rejection	
Balkan nephropathy	
medullary cystic disease	

Factors differentiating Type 1, Type 2, Type 4

	Type 1	Type 2	Type 4
Serum K^+	Low	Low	High
Renal Function	Ⓝ/near normal	Ⓝ/near Ⓝ	Stage 3, 4/5 chronic kidney disease (CKD)
Urine pH During Acidosis	High	Low	Low or high
Serum HCO_3^-	10-20	16-18	16-22
Urine pCO ₂ (mm Hg)	<40	<40	>70
Urine Citrate	low	High	low
Fanconi Syndrome	No	may be present	No

Management

00:37:55

Non-volatile acid 1 mg/kg → To be excreted from the body

A. Sodium Bicarbonate Shohl's Solution 1 meq/ml
 Or
 sodium citrate 1 meq of citrate

5 ml → 500 mg of sodium citrate
 +

640 mg of citric acid

B. Potassium citrate : 5 ml → 10 meq of K^+
 (Citralka) 10 meq of citrate/ HCO_3^-

Severe hypokalemia

Serum $K^+ = 1.5$ meq/l

I.V KCl infusion 1-amp KCl = 10 ml

1 ml = 2 meq

2 amp = 20 meq → increases K^+ by 0.25 meq/l

2 amp KCl 100 ml/hr

In 200 ml NS 1 amp/hr

Over 2 hrs 20 meq/hr x 2 hrs

40 meq → increases K^+ by 0.5 meq/l

Active space

Example: if serum K^+ = 1.5 meq/l $\rightarrow$ target K^+ = 3-3.5

max dose that can be given / day - 240 meq/l

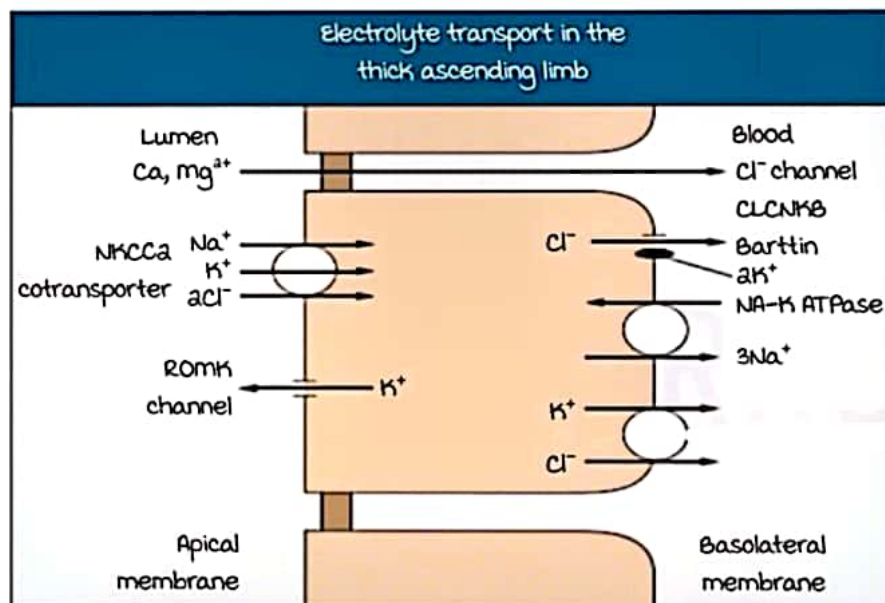
Hypokalemia / urine K^+ loss (alkalosis)

Ⓝ to low BP

- 1) Bartter syndrome
- 2) Gitelman syndrome

High BP

- 1) Conns
- 2) Liddle
- 3) Cushing
- 4) AME (apparent mineralocorticoid excess)
- 5) GRA (glucocorticoid remediable Aldosterone)



- | | | | |
|---|---|---|--------------------|
| Ⓜ | { | $Na^+K^+2Cl^-$ symport (Type 1 Bartter) | Type 5 Bartter |
| | | $ROMK$ channel (Type 2 Bartter) | Hypocalcemia |
| | | $CLCNKB$ (Type 3 Bartter) $\rightarrow$ Survives to Adulthood (classical) | Autosomal dominant |
| | | Bartter (Type 4 Bartter) | |

Type 1

- Volume depletion
- Intravascular depletion
- Vomiting, Failure to thrive, polyuria
- 2° Renin angiotensin system (RAS) $\oplus \rightarrow$ Hypokalemia, alkalosis
 $\rightarrow$ Hypercalcemia $\rightarrow$ Stones
 $\rightarrow$ Hypermagnesuria

Type 3

1. Intravascular volume depletion $\rightarrow$ stimulates prostaglandin(PG)
 $\rightarrow$ stimulates renin
2. Treatment $\rightarrow$ NSAID (indomethacin)
3. Serum Ca^{2+} & $\text{Mg}^{2+} \rightarrow$ normal

Gitelman syndrome

- milder disease (survive into adulthood)

Defect $\text{Na}^+ - \text{Cl}^-$ symporter in DCT

- Less volume depletion
- Less vomiting
- Less hypokalemia
- Less activation of RAS
- No PG stimulation

Ca^{2+} conservation (hypercalcemia, hypocalciuria)

Mg^{2+} absorption $\rightarrow$ Hypomagnesemia

Features Differentiating Bartter and Gitelman's syndrome			
Features	Neonatal Bartter	Classic Bartter syndrome	Gitelman's syndrome
Age at onset	Neonatal period	Infancy / childhood	childhood / later
Maternal Hydramnios	Common	Rare	Absent
Polyuria, polydipsia	marked	Present	Rare
Dehydration	Present	often present	Absent
Tetany	Absent	Rare	present
Growth retardation	Present	present	Absent
Urinary calcium	very high	normal or high	low
Nephrocalcinosis	present	Rare	Absent
Serum magnesium	normal	Occasionally low	low
Urine prostaglandins	very high	high or normal	normal
Response to indomethacin (improvement of hypokalemia And renal salt wasting)	good	good	Rare

HYPERKALEMIA

Introduction

00:00:08

medical emergency

no cardinal manifestations

ECG (to rule out arrhythmia)

patients at risk - CKD or AKI (inability to excrete K^+)

Presents with non specific symptoms like:

- fatigue, syncope, palpitation, giddiness

Neuromuscular manifestations :

1) Paresthesia / weakness

2) $\downarrow$ NH_4^+ production

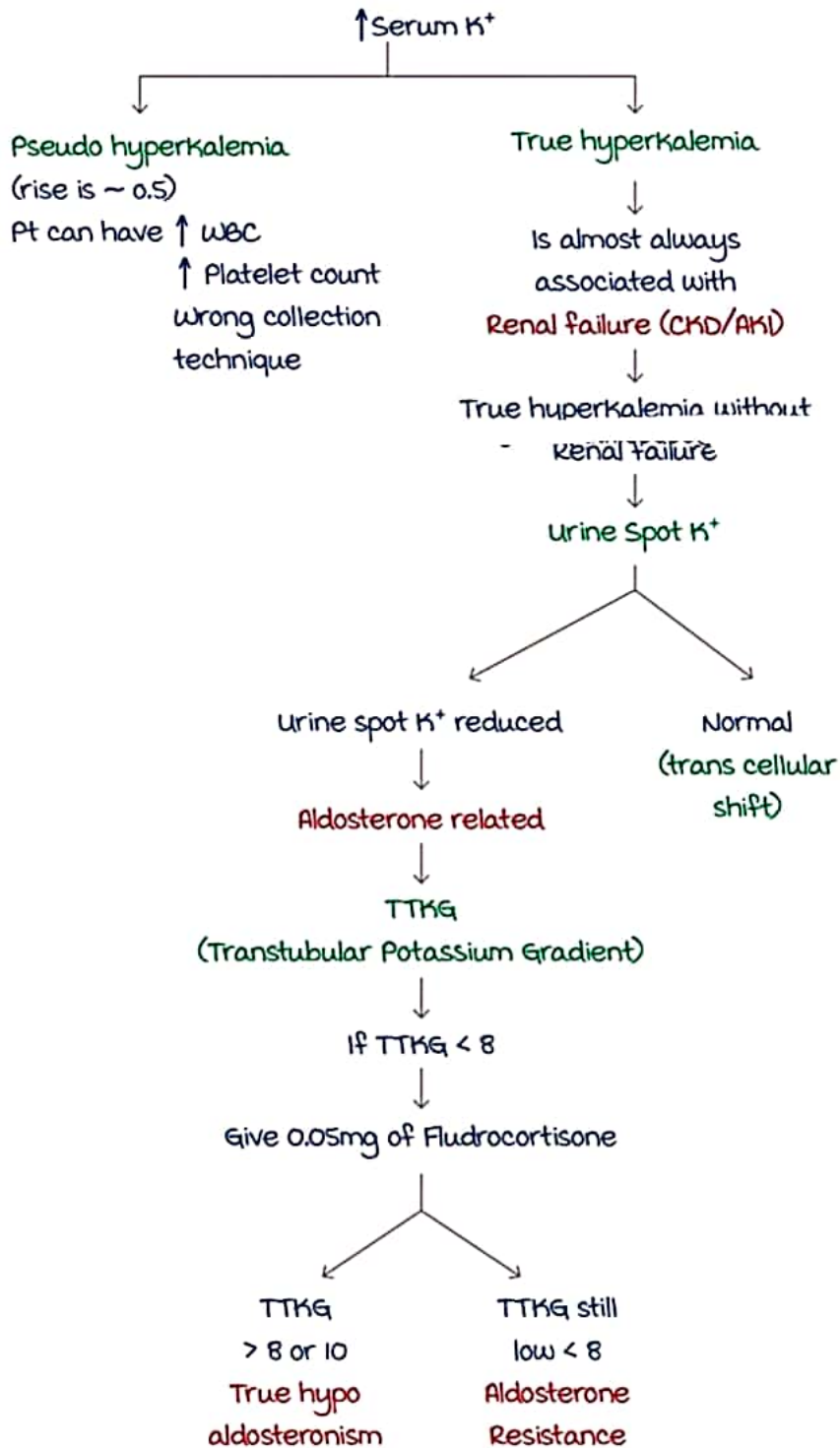
3) $\uparrow$ insulin secretion

ECG changes in hyperkalemia

00:02:04

ECG Changes in Hyperkalemia		
QRS Complex	Approximate Serum Potassium (mmol/L)	ECG Change
 P wave T wave	-4	Normal
	6-7	Peaked T waves
	7-8	Flattened P wave, prolonged PR Interval, depressed ST segment, Peaked T wave
	8-9	Atrial standstill, prolonged QRS Duration, further peaking T waves
	>9	Sine wave pattern

Active space



Transcellular shift is seen in:

- 1) Hyperglycemia
- 2) α agonist, β antagonist
- 3) Exercise
- 4) $\uparrow$ Osmolality
- 5) Tumor lysis syndrome (TLS) / Rhabdomyolysis / Hemolysis

Trans tubular potassium gradient (TTKG)

00:08:00

Normal: 8-12

An indicator of aldosterone activity

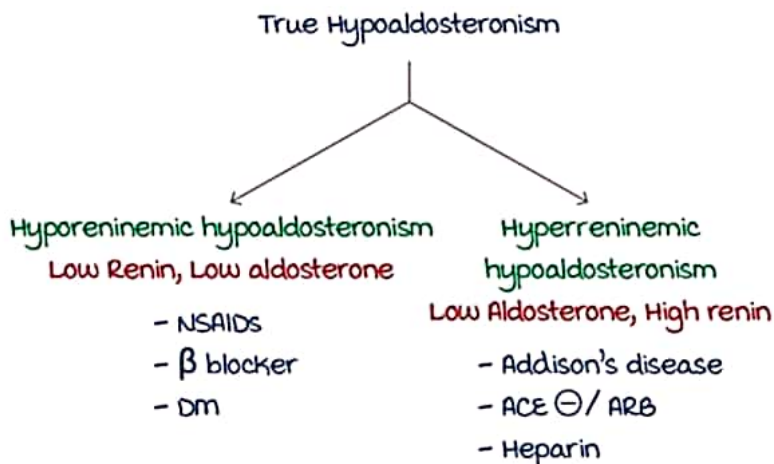
$$TTKG = \frac{\text{Urine Potassium}}{\text{Serum Potassium}} \div \frac{\text{Urine Osmolarity}}{\text{Serum Osmolarity}}$$

$$\left(\text{ie, } \frac{\text{Urine Potassium}}{\text{U osmolarity}} \times \frac{\text{S. Osmolarity}}{\text{Serum Potassium}} \right)$$

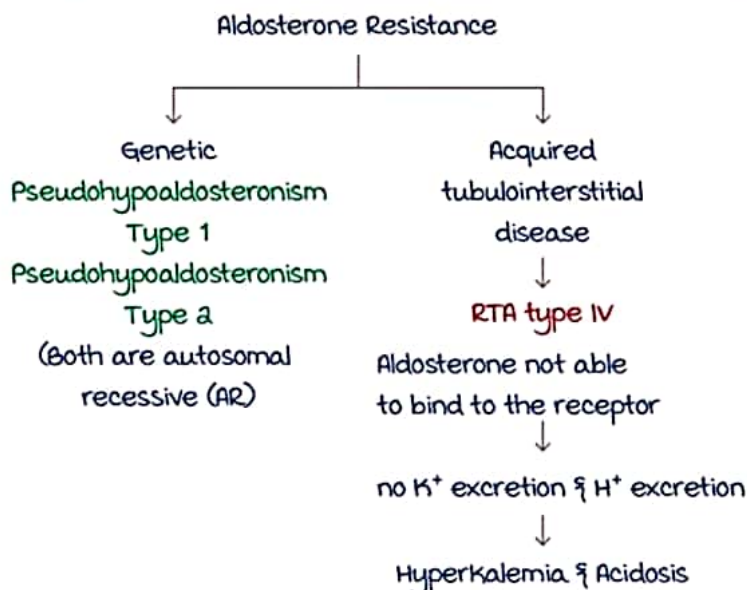
In hyperkalemia, TTKG : 10 to 12

True hypoaldosteronism

00:11:59

**Aldosterone resistance**

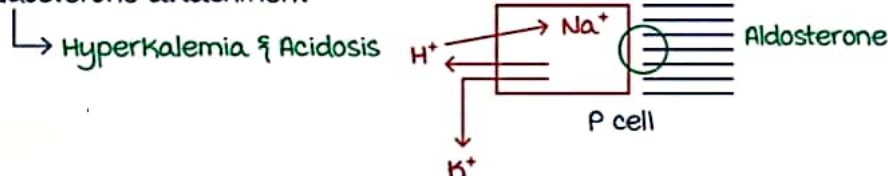
00:15:11



Renal tubular acidosis (RTA) type IV

00:17:30

Fibrosis or injury to the interstitial site of P cell prevents aldosterone attachment



Renal function test(RFT)→ abnormal (mc)

Hyperkalemia is disproportionate to degree of renal failure

- Causes:
- Chronic tubulointerstitial disease
 - SLE
 - Reflux Nephropathy
 - Obstructive nephropathy
 - Sickle cell nephropathy

Drugs associated with RTA Type IV:

- Cyclosporine / Tacrolimus
- Amiloride / Triamterene (ENaC blockers)
- Trimethoprim
- Pentamidine
- Aldosterone antagonist - Spironolactone
Eplerenone

Factors differentiating type 1,2 & 4 RTA

00:20:41

Factors Differentiating Type 1, Type 2 and Type 4 RTA			
	Type 1 RTA	Type 2 RTA	Type 4 RTA
Serum K^+	Low	Low	High
Renal function	Normal or near normal	Normal or near normal	Stage 3, 4 or 5 chronic kidney disease
Urine pH during acidosis	High	Low	Low or high
Serum HCO_3^- (mmol/L)	10-20	16-18	16-22
Urine pCO_2 (mmHg)	<40	<40	>70
Urine citrate	Low	High	Low
Fanconi syndrome	No	may be present	No

In Type 4 RTA:

- Hyperkalemia
- Renal function - Never normal
- urine pH - Variable
- Acidosis $\oplus$
- Hypocitraturia

usually in alkali loading urine $\text{PCO}_2 \uparrow$ via $\text{H}^+ - \text{ATPase}$

In distal RTA - urine PCO_2 fails to $\uparrow$

But in type 4: Urine PCO_2 - Normal

Pseudohypoaldosteronism

00:24:32

Pseudohypoaldosteronism type 1

1. Loss of function mutation of ENaC
(AR)

2. Hyperkalemia

Acidosis

N to low BP

Liddle syndrome

1. Gain of function mutation
of ENaC

2. Hypokalemia

alkalosis hypertension

B. Pseudohypoaldosteronism type 2 v/s

- AR

also known as Gordon's syndrome

3. problem in DCT

- Hyperkalemia

- Acidosis

- HTN

Gitelman's syndrome

- Hypokalemia

- Alkalosis

- normal to Low BP

- Hypokalemia

$\uparrow$ urine K^+

Acidosis



RTA



Type 1

Type 2

- Hypokalemia

$\uparrow$ Urine K^+ , alkalosis



N to Low BP

- Bartter syndrome

Gitelman syndrome



Opposite

Pseudohypoaldosteronism

Type 2

$\uparrow$ BP

- Conn

- Liddle

- Cushing

- Apparent mineralocorticoid
excess (AME)

- Glucocorticoid-remediable
aldosteronism

Opposite to

pseudohypoaldosteronism

Type 1

Drugs causing hyperkalemia

00:29:22

Medications Associated with Hyperkalemia		
Class	Mechanism	Example
Potassium-containing medicines	Increased potassium intake	KCl, PCN K, Polycitra, Polycitra K
β -Adrenergic receptor blockers	Inhibit renin release	Propranolol, metoprolol, Atenolol
ACE inhibitor	Inhibit conversion of angiotensin I to Ang II	Captopril, lisinopril
Angiotensin receptor blocker (ARB)	Inhibit activation of AT-1 receptor by Ang II	Losartan, valsartan, irbesartan
Heparin	Inhibit aldosterone synthase rate-limiting enzyme for aldosterone	Heparin sodium
Aldosterone receptor antagonist	Block aldosterone receptor activation	Spirolactone, eplerenone
Potassium-sparing diuretic	Block collecting duct apical sodium channel, decreasing gradient for potassium secretion	Amiloride, triamterene; certain antibiotics, specifically trimethoprim and pentamidine
NSAID and COX-2 inhibitors	Inhibit prostaglandin stimulation of collecting duct potassium secretion; inhibit renin release	Ibuprofen
Digitalis glycosides	Inhibit Na^+ , K^+ - ATPase necessary for collecting duct potassium secretion	Digoxin
Calcineurin inhibitors	Inhibit Na^+ , K^+ - ATPase necessary for collecting duct potassium secretion	Cyclosporine, tacrolimus

Digoxin also causes hyperkalemia

Treatment of hyperkalemia

00:30:17

ECG



presence of tall T waves → stabilize myocardium



Calcium gluconate

10 ml 10% IV over 10 minutes

10ml has 1g (~93 mg of elemental Ca^{2+})

onset of action : 1-3 minutes §

duration of action : 30 min-1 hr

repeat one more dose in unresponsive cases

To ↑ cellular uptake of K^+ → Insulin dextrose infusion



10 units of regular insulin IV followed by
500 ml of 50% dextrose slowly over 1 hr

Or

10 units of Insulin in 100 ml of 25%
dextrose & run it over 1 hr

(onset of action 30 min acts for 4-6 hr)

Nebulised Salbutamol

- 10-20mg

As an adjuvant therapy (never given as monotherapy)

- onset of action 30 min & stays for 2-4 hrs

For K^+ Removal → Sodium or Calcium (K Bind)

Polystyrene sulfonate



not used due to increased risk of intestinal
perforation

Dialysis - Is the last option

New drugs: Patiromer, Zirconium Cyclosilicate

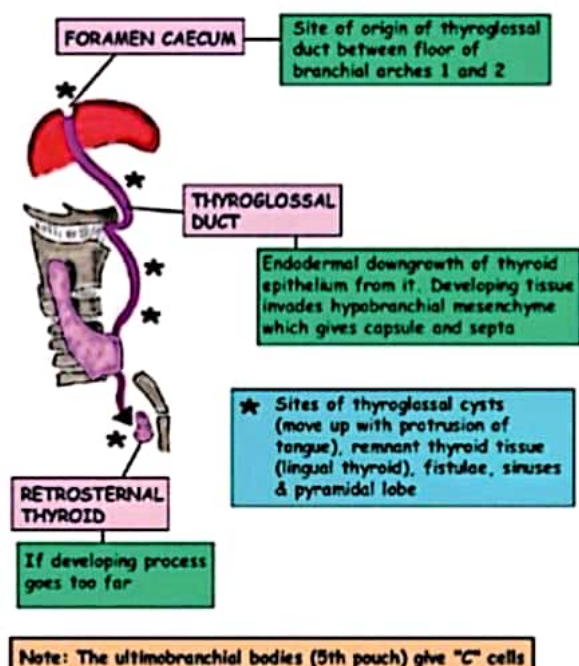
THYROID BASICS

Development of thyroid

00:01:24

- Starts at 3rd week of Intrauterine life
- it is an endodermal derivative
- Endodermal cells arises from the floor of Primitive pharynx

Thyroid Development



- From Foramen Caecum, it Begins as a diverticulum which elongates to form Thyroglossal duct /tract
- Thyroglossal tract usually disappears and in some patients remnants give rise to Thyroglossal Cyst
- From Thyroglossal tract, it migrates towards thyroid
- Structural and functional unit of Thyroid gland

Thyroid follicle

- Adjacent to follicle, Para-follicular cells are present .
- Para-follicular cells are C - cells derived from the ultimobranchial body (neural crest cell)
- Para-follicular cells produce Calcitonin
- follicular cells produce T_3, T_4
- Hormone Synthesis starts at 11 weeks of IuF

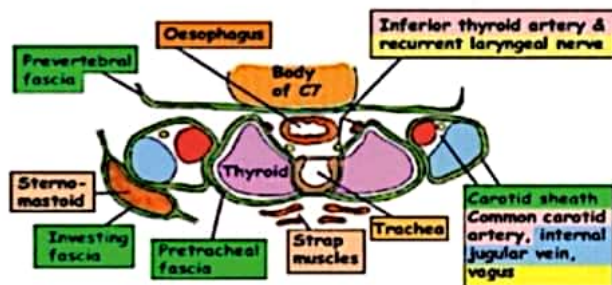
THYROID GLAND - AXIAL SECTION AT C7

Relations of thyroid gland

Posterior: Prevertebral fascia, carotid sheath, parathyroids, trachea

Medial: Recurrent laryngeal nerve, trachea, larynx, oesophagus

Anterior: Pretracheal fascia, sternohyoid, sternothyroid venous arch



Anatomical Relations :

Anteriorly : Sternohyoid

Sternothyroid

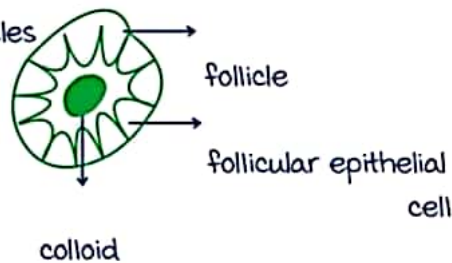
Posteriorly : Carotid sheath

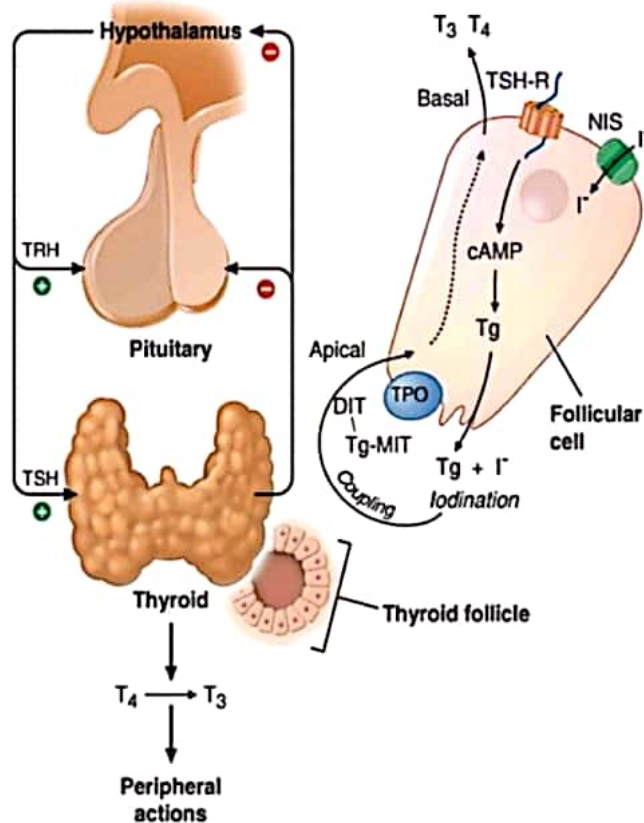
medially : Recurrent laryngeal nerve
oesophagus

Hormone synthesis

00:07:24

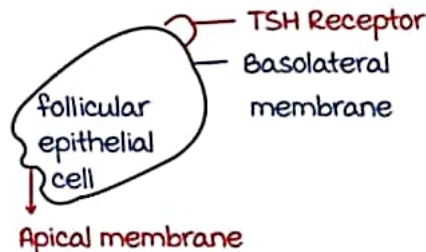
- Thyroid Gland has numerous follicles
- follicles contains follicular epithelial cells
- In the centre of the follicle, colloid Present .
- Inside the colloid, hormones are stored (2 - 3 months)





Follicular epithelial cell :

- it has two surfaces
 - 1) Basolateral membrane
 - 2) Apical membrane
- TSH receptor is present on the Basolateral membrane
- TSH stimulates the gland to produce Thyroid hormones
- Although TSH is required for the proper functioning of thyroid gland, Thyroid can produce Thyroid hormones even in the absence of TSH.



That is why, In Pituitary insufficiency & Adult hypopituitarism hypothyroidism is not prominent

- TSH binds to TSH Receptor
- Dopamine & Steroids } competes with TSH to bind to TSH Receptor
- On binding of TSH to TSH receptor

Step - 1 : Iodide uptake :

- Iodide uptake into the follicular epithelial cell through Na⁺ - I Symporter (Sodium - Iodide Symporter)

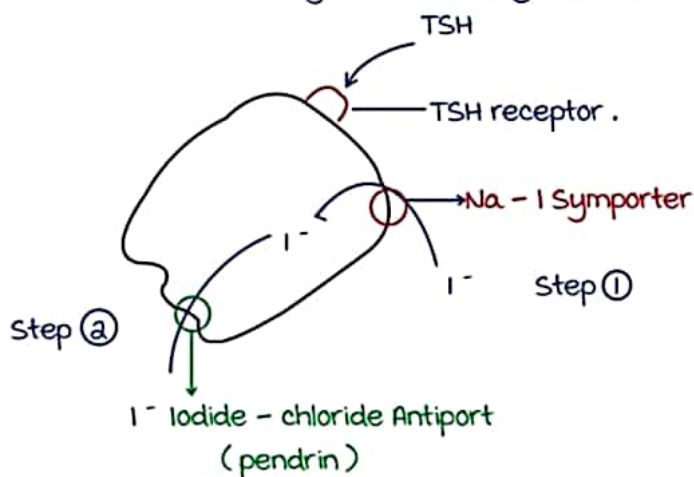
- **Na - I Symporter** can be seen in
Breast
Salivary gland
Thyroid
Placenta
- To visualise Thyroid gland, we do Radioisotope scan
- In Radioisotope Scan (Thyroid Scintigraphy) use isotope of Iodine I^{133}
- I^{133} also enters Thyroid through **Na - I Symporter**
- Now, Technetium 99 has replaced I^{133}

Inhibitors of Na - I Symporter :

- 1) Thiocyanate
- 2) perchlorate

Step - 2 Iodide Crossing Apical membrane :

- Iodide crosses apical membrane via Iodide - chloride antiport (also known as pendrin)
- This pendrin also present in the inner ear
- **Pendred Syndrome**
Goitre with Sensory Neural Hearing Loss (SNHL)



Step - 3 Organification of Iodine :

- Conversion of $I^- \rightarrow I_2$ done by enzymes
Present on Apical membrane
 - 1) Thyroid Peroxidase (TPO)
 - 2) Dual Oxidase (Duox)
- Drugs Inhibiting Thyroid Peroxidase
↓
Thionamides

Step - 4 Iodination :

- Inside the colloid , thyroid hormone precursor molecule is present
→ **Thyroglobulin**
- it has Tyrosine residues
- Iodine is attached to the Tyrosine residue of **Thyroglobulin** to form MIT or DIT

Step - 5 Coupling :

- MIT Combines with DIT → T_3
 - DIT Combines with DIT → T_4
- } under the control of **Thyroid Peroxidase (TPO)**
- Very small amount of DIT combines with MIT
 $DIT + MIT \rightarrow \text{reverse } T_3 \text{ (very little)}$
 - physiologically not significant .

Step - 6 Hormone release :

- Thyroglobulin with the hormones taken back into the epithelial cell
- undergoes **Proteolysis** , T_3 & T_4 are released into Blood stream
- **Thyroglobulin** is taken back into colloid
- hormone release is inhibited by **Iodides**
- Physiologically , most Important hormone is T_3

Last Step Conversion of $T_4 \rightarrow T_3$:

- Peripherally T_4 gets converted to T_3 by enzyme **Deiodinase**
 $T_4 \xrightarrow{\text{Deiodinase}} T_3$
- urinary Iodide levels are $\geq 100 \mu\text{g} / \text{l}$ in urine replete Population

Age	RDA of iodine ($\mu\text{g}/\text{day}$)
0-5 years	90
6-12 years	120
>12 years	150
Pregnancy and lactation	250

Table 38-1. Summary of Thyroid Hormone Kinetics.

Variable	T_4	T_3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 μg	54 μg
Daily production	75 μg	25 μg
Fractional turnover per day	10%	60%
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 day
Serum levels		
Total	5-11 $\mu\text{g/dL}$ (64-132 nmol/L)	95-190 ng/dL (1.5-2.9 nmol/L)
Free	0.7-1.86 ng/dL (9-24 pmol/L)	0.2-0.52 ng/dL (3-8 pmol/L)
Amount bound	99.96%	99.6%
Biologic potency	1	4

- Daily production of T_4 is 3 times more than T_3
- Fractional Turnover of T_3 is 60 % but T_4 is 10 %
- Clearance of $T_3 \gggg T_4$
- Serum $t_{1/2}$
 - T_3 - 1 day
 - T_4 - 7 days (pharmacologically Important)
- Potency $\rightarrow T_3$ is 4 times potent than T_4
- Bound form
 - $T_4 \rightarrow 99.96\%$
 - $T_3 \rightarrow 99.6\%$
- Free form of T_3, T_4 is the metabolically active form
- So, the free form
 - $T_3 - 0.4\%$
 - $T_4 - 0.04\%$

Deiodinases :

- Converts T_4 to T_3 Peripherally
- Deiodinase I - Thyroid, Liver, Kidney
- Deiodinase II - Thyroid, pituitary, brain
- Deiodinase II - has more affinity to T_4 than Deiodinase I

- $T_4 \rightarrow T_3$ Conversion by Deiodinases is inhibited (I & II)

In fasting state, Systemic illness
Acute Infection
Oral Contrast

- Deiodinase III $\rightarrow$ Normally seen in placenta only
- it is activated in muscle and Liver in following conditions
fasting state
Systemic illness
acute infection
oral Iodinated Contrast
- where in these Conditions Deiodinase I & II are inhibited.
- So, By the action of Deiodinase III
 $T_4 \xrightarrow{\text{Deiodinase III}} \text{reverse } T_3$

Drugs Inhibiting Deiodinase :

- 1) β - Blocker - Propranolol
- 2) PTU
- 3) Amiodarone
- 4) Steroids

- Don't measure T_3 , T_4 levels in
 - fasting
 - Systemic illness
 - acute infection
 - oral contrast

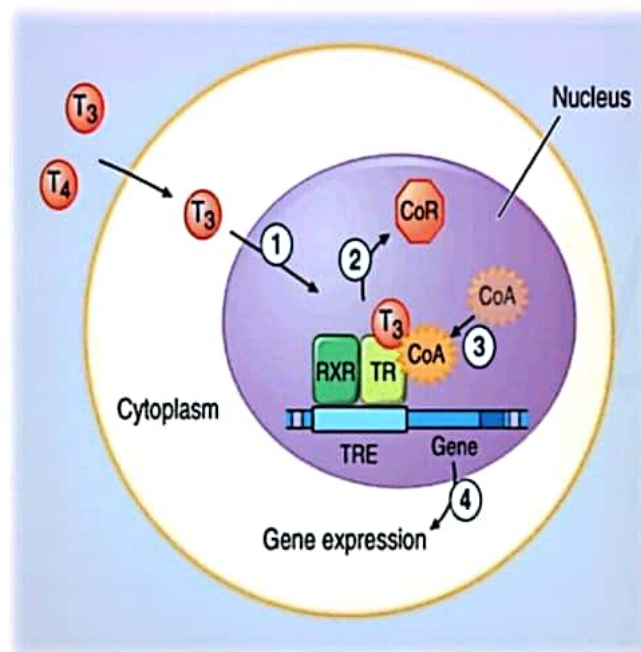
because they show false values

- here, reverse T_3 is formed in excess.

But it is clinically insignificant
because patient is Euthyroid

Thyroid Hormone Receptor :

- TSH Receptor
↓
cell membrane
receptor
acts via cAMP
- T_3/T_4
↓
Intranuclear
receptors

Figure 341-4 Mechanism of Thyroid Hormone Receptor Action.

- T₃ & T₄ are bound to 3 proteins
 - a) Thyroid binding globulin (70 %)
 - b) Albumin (20 %)
 - c) Transthyretin (10 %)
 also known as Prealbumin – also carries Vitamin – A

Euthyroid hyperthyroxinemia

00:36:36

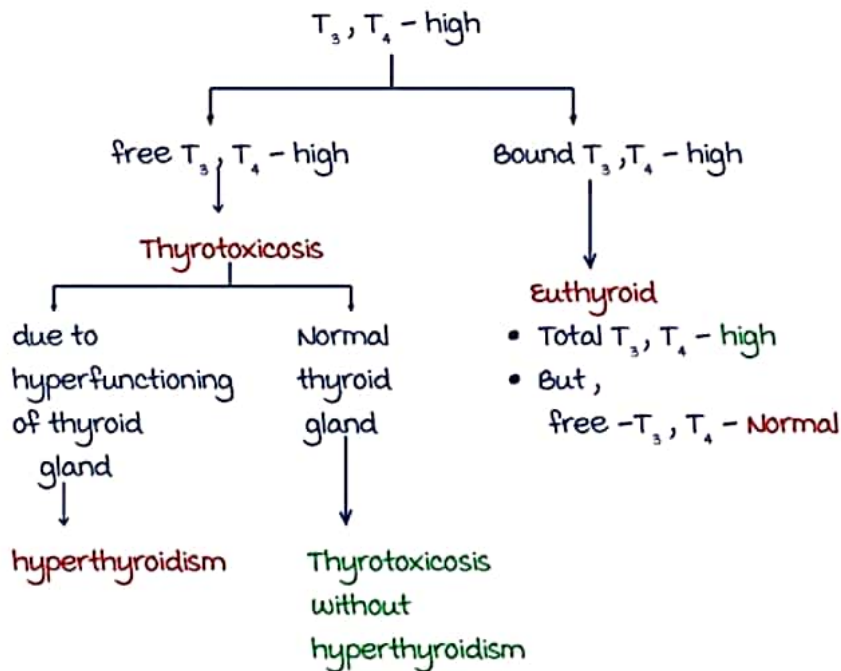
TABLE 405-3 CONDITIONS ASSOCIATED WITH EUTHYROID HYPERTHYROXINEMIA

Disorder	Cause	Transmission	Characteristics
Familial dysalbuminemic hyperthyroxinemia (FDH)	Albumin mutations, usually R218H	AD	Increased T ₄ Normal unbound T ₄ Rarely increased T ₃
TBG			
Familial excess	Increased TBG production	XL	Increased total T ₄ , T ₃ Normal unbound T ₄ , T ₃
Acquired excess	Medications (estrogen), pregnancy, cirrhosis, hepatitis	Acquired	Increased total T ₄ , T ₃ Normal unbound T ₄ , T ₃
Transthyretin^a			
Excess	Islet tumors	Acquired	Usually normal T ₄ , T ₃
Mutations	Increased affinity for T ₄ or T ₃	AD	Increased total T ₄ , T ₃ Normal unbound T ₄ , T ₃
Medications: propranolol, ipodate, loproloic acid, amiodarone	Decreased T ₄ → T ₃ conversion	Acquired	Increased T ₄ Decreased T ₃ Normal or increased TSH
Resistance to thyroid hormone (RTH)	Thyroid hormone receptor β mutations	AD	Increased unbound T ₄ , T ₃ Normal or increased TSH Some patients clinically thyrotoxic

^aAlso known as thyroxine-binding prealbumin (TBPA).**Abbreviations:** AD, autosomal dominant; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; XL, X-linked.

Hyperthyroxinemia:

- T_3 or T_4 is high (may be free or bound)



- Total T_3, T_4 , has no value
- only free T_3, T_4 is useful

So, in Euthyroid Hyperthyroxinemia

Total T_3, T_4 - high
 Bound T_3, T_4 → high
 free T_3, T_4 → Normal
 TSH - Normal

Causes of Euthyroid Hyperthyroxinemia:

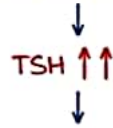
1) Thyroid Binding globulin excess:

- it can be familial - X-linked Recessive
- or
- Acquired - seen in Pregnancy
 estrogen
 viral hepatitis

2) Resistant to Thyroid hormones (RTH)

- Autosomal Dominant Condition
- Resistant to Thyroid Receptor Beta due to mutation
- Partial resistance produces Euthyroid Hyperthyroxinemia
- most of the patients are Euthyroid

- hormones are not binding to receptor



But, patient clinically euthyroid

- Rarely, this TSH may again stimulate hormone Synthesis

↓
T3, T4 Synthesised acts on

α - receptors (which are sensitive)

↓
Rarely, may go into Thyrotoxicosis

- TSH - may increase T3, T4 (free)

↓
acts on α - receptor causes Thyrotoxicosis

- heart rate increases
- Goitre
- Attention deficient Hyperactive disorder
- mild reduction in IQ

Thyroid hormone actions

00:46:09

- maintains ' Basal Metabolic Rate '.

1) Carbohydrate metabolism :

1) Increases glucose uptake in tissues

2) Increase
 • gluconeogenesis
 glycogenolysis
 } ↑ Glucose

- That is why in myxedema Coma, which is an Extreme form of Hypothyroidism

↓
myxedema coma patient
suffers from Hypoglycemia

2) Protein metabolism :

- Catabolic action → Proteolysis
- patient get myopathy
osteopenia
Hypercalcemia
Hypercalcuria / stones

3) Fat metabolism :

- Increases **Lipolysis** .
- Increases clearance of **cholesterol**
- Because of this , hypothyroid patient has **Hypercholesterolemia**
- Any patient who is having **Hypercholesterolemia**



1st rule out **Hypothyroidism**

4) Increases O_2 Consumption Everywhere except **Brain & Gonads** .

5) With respect to Electron Transport chain



Thyroid hormones are uncouplers of
oxidative phosphorylation



No ATP formed

Shift towards 'Thermogenesis'

- That is why in a myxedema Coma , patient has **Hypothermia**

myxedema Coma → Extreme Hypothyroidism

1) Hypoglycemia

2) Hypothermia

6) Growth :

- for Bone growth
- CNS - myelination

7) Heart :

- **Indirect action**
- Increases the Sensitivity to **Catecholamines**

- Bone protein mobilisation due to $\uparrow T_3 / T_4$



results in **osteoporosis**

8) Liver :

- It converts
 β - Carotene → Vitamin A
- also stimulates **Erythropoiesis** .

TFT AND HYPOTHYROIDISM

Thyroid Function Test

00:00:14

- TSH → Done while fasting
- Free T_3/T_4 → no relation to food

TSH	T_4	FT_4	T_3	FT_3	Condition
↑	N	N	N	N	Subclinical hypothyroidism; Recovery from Acute illness
↑	↓	↓	↓	↓	Primary hypothyroidism
↑	↑	↑	↑	↑	Thyroid hormone resistance / Thyroid adenoma
Normal Or ↓↓	↓	↓	↓	↓	TSH appropriately Normal; Secondary Hypothyroidism
↓	N	↑	N	↑	Thyrotoxicosis / H.mole / Pregnancy

Basics of TFT interpretation

00:08:38

- A normal TSH excludes primary abnormality of thyroid function
- T_3 toxicosis is present in 2–5% and hence free T_3 is measured for everybody with suppressed TSH and normal free T_4
- Serum thyroglobulin levels are increased in all types of thyrotoxicosis except thyrotoxicosis factitia
- Causes of elevated / decreased TBC can be interpreted

Primary hypothyroidism:

↓ Free T_3 ; Free T_4 ↓
TSH ↑↑

Primary hypothyroidism - if suspected due



Exclude autoimmune causes by antibodies tests



- | | |
|--------------------------------|--------------------------------|
| 1. Thyroid peroxidase Antibody | } Positive in autoimmune cause |
| 2. Anti thyroglobulin | |
| 3. Anti microsomal | |
| 4. Anti TSH receptor | |

- m/c cause for autoimmune primary hypothyroidism is "Hashimoto's Thyroiditis"

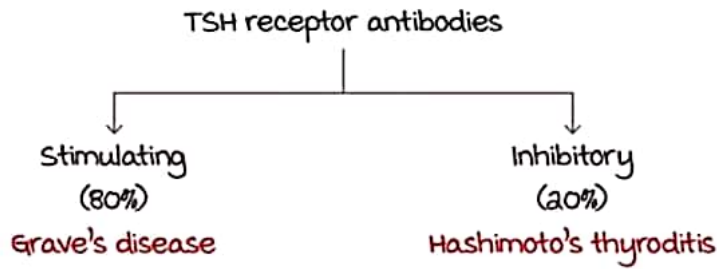
Drugs and TFT

00:12:10

Steroids Propranolol Iodine Amiodarone Propylthiouracil	Inhibitors of Deiodinase 1 and 2
Phenytoin Carbamazepine Rifampicin Sertaline Ritonavir	Enzyme Inducers ↑se metabolism of free T_4 eg: The metabolism eltroxine
Lithium D_a blockers Clomiphene Spironolactone	↑se TSH (hypothyroidism)
$Al(OH)_3$ Cholestyramine Calcium carbonate Ferrous sulfate	↓se Thyroid Hormone absorption

Antibodies:

Anti - T_{PO} (Thyroid peroxidase) or microsomal or TSH are seen or TSH are seen in 100% patients with autoimmune hypothyroidism and 80% with Grave's disease



20% have TSH receptor blocking antibodies whereas Others have Thyroid stimulating immunoglobulin TSI which is responsible for Graves disease

Excess iodide transiently inhibits thyroid Hormone synthesis for 5 to 7 days followed by thyroid escape phenomenon called "Wolff chaikoff effect"

Hypothyroidism

00:16:07

Primary Hypothyroidism:

- Autoimmune
Hashimoto's thyroiditis
- Iodine deficiency
- Post operative
- Congenital hypothyroidism
- Drugs [Lithium; clomiphene; Dablocker; Spironolactone; IFN- α]

Secondary hypothyroidism:

Due to pituitary

Hashimoto's thyroiditis

00:18:04

- Autoimmune thyroiditis/illness
- Female >> male
- middle aged females [mean age of 60 yrs]
- m/c cause for primary hypothyroidism-Other autoimmune illness associated

Type 1 DM
Perinicious anaemia
vitiligo
SLE
Addison

- HLA DR-3 ; HLA-DR -4; DR -5
CTLA₄ polymorphisms
[Cytotoxic T -lymphocyte Associated Antigen]
-PTPN .. polymorphisms
- most of the patient presents with Goitre
[Irregular; firm and heterogenous enlargement of gland]
- ↑es risk of premalignant condition
 - Extranodal marginal Zone lymphoma [B-cell]
 - Papillary carcinoma of thyroid

Histology:

- Lymphocytic infiltration with germinal centre formation
- Atrophy of follicles with oxyphil metaplasia or oxyntic cells
- Hurthle cell with eosinophilic cytoplasm
- Absence of colloid
- mild fibrosis

Symptoms of hashimoto's thyroiditis

00:23:29

Thyroid hormone maintains basal metabolic rate

Deficiency causes :

- Generalized slowing of metabolic process [m/c in both primary and secondary hypothyroidism]
- Fatigue [m/c]
- Slowing of speech
- Cold intolerance
- Constipation
- Weight gain [m/c]
- Delayed relaxation of DTR (deep tendon reflexes)
- Decreased heart rate
- Hair loss

TSH ↑↑ → Stimulate fibroblasts and Glycosaminoglycans
and | [Hyaluronic acid]
↓T₄

Trap water

[it causes symptoms of myxedema]

Accumulation of matrix [GAGs] inside Interstitial space of many tissues

- Puffiness
- macroglossia
- Non - pitting edema
- Periorbital edema

myxedematous symptoms in hypothyroidism are

mostly due to
Hypothyroidism

$\left[\begin{array}{c} \text{TSH} \uparrow \uparrow \\ \text{and} \\ \text{T}_4 \downarrow \end{array} \right]$

Excess of TSH is seen in primary

These symptoms which are commonly seen in Primary hypothyroidism



Complications of hypothyroidism

00:28:37

- m/c menstrual abnormality Oligomenorrhoea (or) Amenorrhoea/infertility
- Obstructive sleep apnea syndrome due to **macroglossia**
- Weight gain and unexplained constipation
- Pericardial effusion
- Decreased pulse rate
- Decreased exercise capacity
- Shortness of breath
- Hypercholesterolemia
- Rarely menorrhagia
- **Dry coarse skin**

Presentation:

- Goitre → **Firm and non tender**
- Tiredness / Poor concentration / Weight gain / Hair loss
- menorrhagia / Infertility
- **Dry coarse skin / Delayed DTR / myxedema / Bradycardia**
- Periorbital puffiness + Hoarse voice + Non pitting edema + macroglossia ⇒ **primary hypothyroidism**

Approach and subclinical hypothyroidism

00:31:09

1. **m/c combination possible**—High TSH and Low free T4 seen in excess intake of drug

Low T4 **on drugs** ↑ TSH (interprets disease)
 ↑ TSH —————→ ↑ T4 (excess drug)

2. High TSH and high FT₄ shows that the patient was on treatment and the treatment is not correct.
3. High TSH ; Normal free t4 → **Sub clinical hypothyroidism**

4. Anti - TPO → Hashimotos Thyroiditis

5. Normal TSH and $\uparrow T_4$ This combination is not possible

Subclinical hypothyroidism

00:34:00

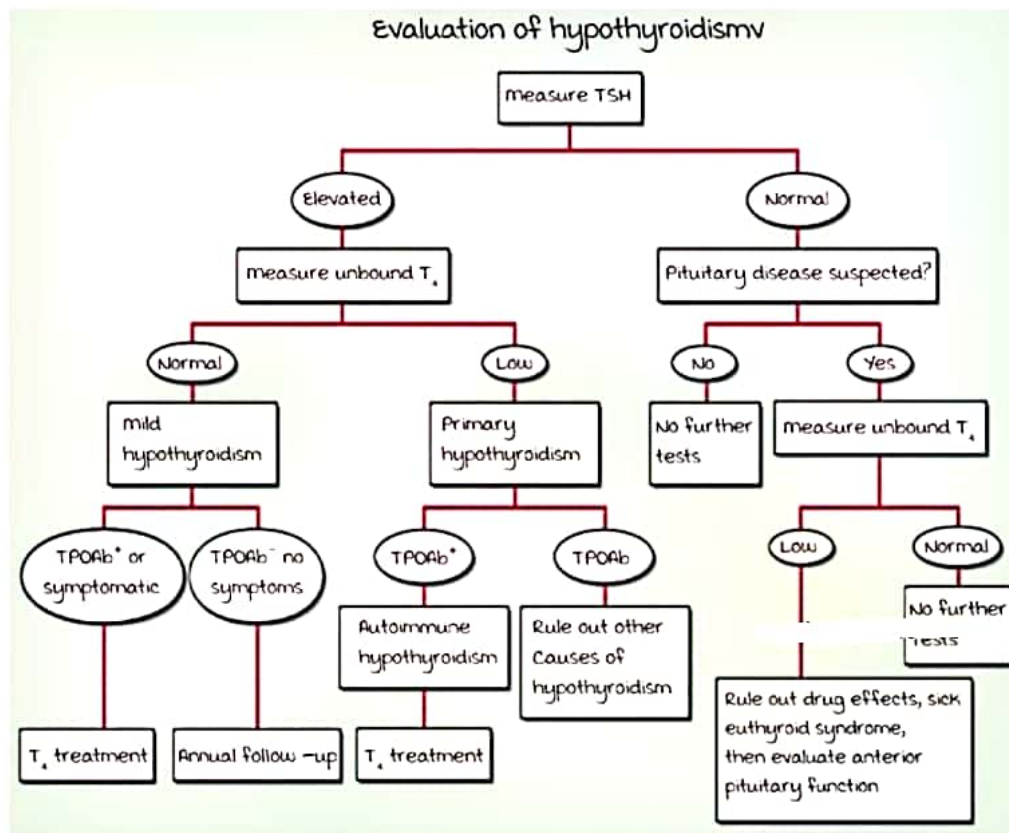
TSH upper limit → 5 milli IU/litre

5-10m IU/L → High normal

Sub clinical hypothyroidism → $\uparrow$ cardiovascular mortality

Indications for subclinical hypothyroidism treatment :

1. TSH > 10m IU/L
2. Symptoms
3. Pregnant
4. Antibodies positive



In, hypothyroidism proximal myopathy + pseudo-hypertrophy of calf seen called "Hoffman's syndrome"

- Eltroxin 1.7 mg/kg/day
- Preferably at 7 am in the morning on an empty stomach followed by food intake 30 min later
- In Elk diac disease →
25 mg/day
- Follow up after 8 -12 weeks
if the patient misses the drug in between follow up
the results show $\uparrow$ TSH and $\uparrow$ T₄
- TSH will take minimum 12 -16 weeks to normalize
- Clinical relief 3 -6 months after TSH normalizes
- For monitoring the patient → TSH is the best choice
- m.C.C For Treatment failure → "Non - compliance"

Myxedema coma

00:46:09

40% mortality

Seen in long standing hypothyroid

triggered by



Infection

Extreme Non compliance

MI/Stroke

Presentation:

Reduced consciousness/seizure

1) Hypothermia

2) Hypoglycemia

3) Hypoventilation [$\uparrow$ PCO₂]

4) Hyponatremia [$\uparrow$ ADH]

5) Bradycardia [$\downarrow$ Cardiac output]

Treatment:

- IV T₄ + IV T₃
- Steroids (Hydrocortisone 100mg IV Q8h)
- Eltroxine 500 mg.v followed by 50 - 100 mg/day
- I.V T₃ 5 - 20 mg.v → [if IV is not possible- given Through Ryle's tube]
- Avoid hypotonic fluids

- Eltroxin 1.7 mg/kg/day
- Preferably at 7 am in the morning on an empty stomach followed by food intake 30 min later
- In elderly people (> 60yrs) or cardiac disease → 25 mg/day
- Follow up after 8 -12 weeks
if the patient misses the drug in between follow up the results show ↑TSH and ↑T₄
- TSH will take minimum 12 -16 weeks to normalize
- Clinical relief 3 -6 months after TSH normalizes
- For monitoring the patient → TSH is the best choice
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- IV T₄ + IV T₃
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- Eltroxine 500 mg.v followed by 50 - 100 mg/day
- I.V T₃ 5 - 20 mg.v → [if IV is not possible- given Through Ryle's tube]
- Hypertor [200mg]
- Avoid hypotonic fluids

Hashimoto's encephalopathy [old term]

SREAT [Steroid responsive encephalopathy with auto immune thyroid disease] [New Term]

- Auto immune vasculitis unrelated to thyroid function
- Hashimoto's encephalopathy can occur with a normal TFT
- HLA - B -8 associated
- Elevated antibody titres

Presentation:

Sub acute onset of confusion / Altered level of consciousness

Or

Seizure / myoclonus

Or

Small vessel stroke

- Good response to steroids
- Treatable condition

Other point of Hashimoto's Encephalopathy :

- Anti enolase antibody
- Can occur in euthyroid state
- Stroke like pattern or slowly progressive cognitive

Impairment with Dementia ; confusion or Hallucinations

- Background slowing on EEG
- Steroid responsive

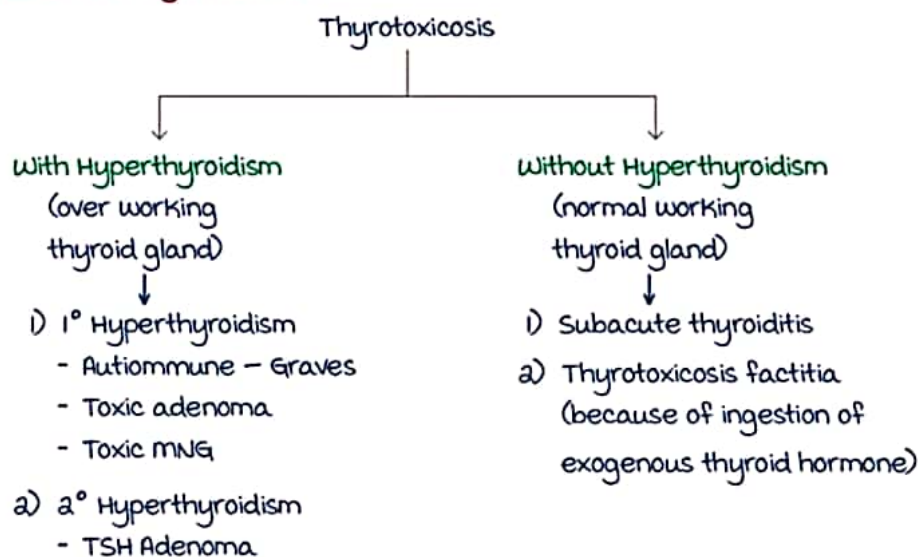


THYROTOXICOSIS

Introduction

- Increase in free or total T_3/T_4 is known as Hyperthyroxinemia
- Increase in free T_3/T_4 , with clinical symptoms is K/a Thyrotoxicosis
- Increase in total T_3/T_4 , person remains euthyroid (seen in Resistance to thyroid hormone & TBG excess)

Causes for thyrotoxicosis



- Cause of hyperthyroidism, thyroglobulin levels are elevated, except in Thyrotoxicosis Factitia (thyroglobulin levels are not elevated)
- Thyroglobulin levels are also checked during Followup of Papillary ca. thyroid after surgery

- Free T_3/T_4 ↑
 - TSH ↓
- } 1° hyperthyroidism → Check for Autoimmune causes (Graves)

↓

TPO Ab
Tg Ab
microsomal Ab
TSH-R Ab

} Any 1 will be +ve in 80% cases

- Free T_3/T_4 ↑
 - TSH ↑
- } 2° Hyperthyroidism

- Free T_4 - n
 - Free T_3 - $\uparrow$
 - TSH Suppressed
- } T_3 Thyrotoxicosis (2% cases)

Graves disease

00:07:06

- mc cause of thyrotoxicosis - 75%
- 20-50 years
- Females > males (4:1)
- Autoimmune
- Associated with HLA DR_a , $CTLA_4$ & $PTPN_{aa}$

Risk factors:

- Smoking
- Post partum
- HAART

Jod basedow effect:

- Iodine supplementation in deficient areas, in a patient with a nodule or TSH-R Ab causing thyrotoxicosis is called as jod basedow effect

Antibodies:

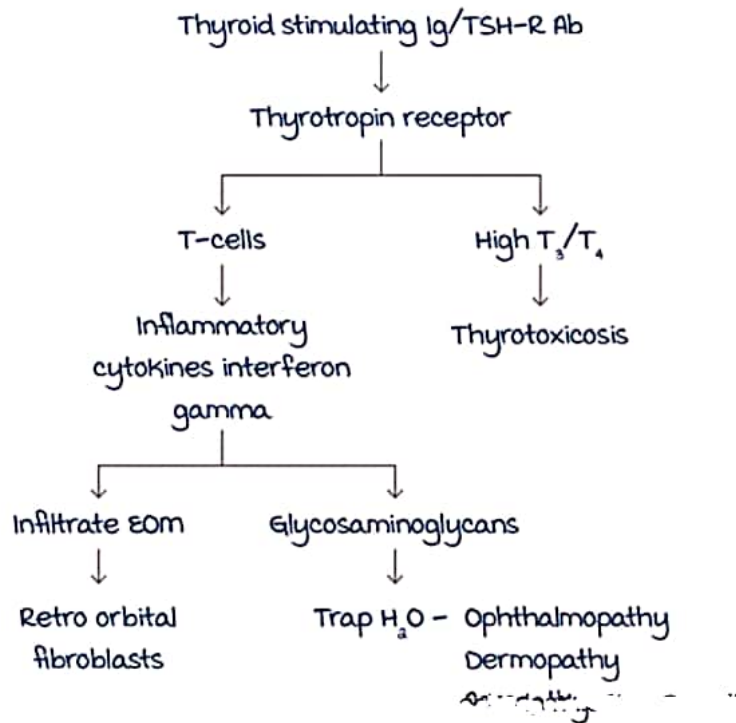
- Thyroid stimulating Ig
- TPO
- Thyroglobulin - 80%
- TSH - R Ab

Difference between thyrotoxicosis and grave's disease

00:11:03

- Ophthalmopathy - severe proptosis
- Dermopathy - Pretibial myxedema with nodular lesions /plaques
- Acropathy - Clubbing





- mc clinical sign in Thyroid ophthalmopathy - lid retraction
 - 1 Kocher's sign : Staring appearance on fixation
 - 2 von Graefe sign : Eyelid lags behind eye ball on attempted down gaze
 - 3 Joffroy sign : Absent forehead creases on upgaze
 - 4 Stellwag : Decreased blinking
 - 5 Dalrymple : Widening of palpebra fissure on fixation
 - 6 Mobius : Poor convergence

Graves disease- clinical features

00:17:05

- Rapid weight loss inspite of increased appetite
- Panic attack with Hyperactivity, Nervousness, tremulousness; tachycardia
- Hypokalemic periodic palsy
- Elderly with Fatigue & weightloss - Apathetic thyrotoxicosis
- Proximal myopathy without fasciculations
- New onset Atrial fibrillation / Worsening of Heart failure
- Heat intolerance; warm & moist skin
- Diarrhea, Polyuria, oligomenorrhea, Loss of Libido
- Gynecomastia
- Depression
- Impaired sexual function
- Osteopenia
- Hypercalcemia

On palpation:

- Diffusely enlarged gland, firm but not nodular
- Warm, moist skin

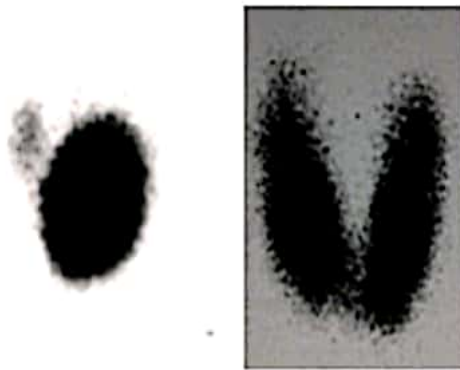
NO SPECS classification of thyrotoxicosis and thyroid scintigraphy

00:22:39

- N - No signs, only symptoms
 - O - only signs
 - S - Soft tissue involvement
 - P - Proptosis
 - E - EOM
 - C - Corneal involvement
 - S - Sight loss
- T_3/T_4 ratio >20 is absolutely in favour of graves
 - Hypercalcemia, Hyperglycemia, Elevated ALP, Leucocytosis, LFT elevated

Thyroid scintigraphy:

- Previously done by I_{131} , now its done by Tc 99
- In graves, B/L diffuse increased uptake



Treatment of graves disease

00:26:09

- First line - Antithyroid drugs
- 50% of cases achieve remission with Anti thyroid drugs
- mostly used are Thionamides
 - Propylthiouracil (PTU)
 - methimazole
 - Carbimazole
- PTU $T_4 \rightarrow T_3$ conversion

TPO Inhibitors

PTU:

- Deiodinase $\ominus$, TPO Inhibitor
- 75% plasma protein binding & No Transplacental passage
- In Pregnancy - DOC. (PTU)
- very short $t_{1/2}$: 1-2hrs - multiple doses
- Extremely Hepatotoxic
- Carbimazole commonly used
- Carbimazole has no protein binding
- Transplacental passage is high
- $t_{1/2}$ - 6 - 8 hours - 5 mg thrice daily - K/a titration
- methimazole can cause Aplasia cutis, choanal atresia if used in pregnancy
- Half life of methimazole is 6hrs and is an irreversible inhibitor
- Beta blockers are given along with these - propranolol 40mg 6th hourly

Active space

Follow - up:

- Dose titration at 4-6 weeks depending on Free T_4 levels
- Approximately 30-60% achieve remission in 12-18 months
- Common S/E of carbimazole is Rash
- most dangerous S/E of carbimazole is Agranulocytosis
- Other S/E - cholestasis/drug induced lupus

Relapse or unable to achieve remission:

- Radio iodine is used for relapse or unable to achieve remission
- Radio iodine is C/I in
 1. Child
 2. Pregnancy
 3. Active eye disease
- With Radio iodine, there is no increase in risk of cancer
- 10% risk of permanent hypothyroidism
- I^{131} is used for Radiotherapy
- I^{123} - Scintigraphy
- I^{125} - Brachytherapy / Radioimmuno assay
- TSH is now estimated by chemiluminescence assay; Previously by Radioimmunoassay
- I^{127} - Normal Iodine
- I^{131} - Radio Iodine

Surgery in graves disease

- Biopsy suspicious of malignancy in nodule
- Hyper parathyroidism
- Pregnancy / Lactation
- Young children
- Compressive symptoms
- 1 month prior to Radio Iodine, Antithyroid drugs to be given to achieve full euthyroidism, to prevent thyroid storm
- Severe ophthalmopathy requires therapy with steroids
- Sub total thyroidectomy is the most performed surgery

Thyrotoxicosis crisis/storm

00:36:50

- Precipitator:
 - Acute illness
 - Radio iodine
 - Surgery
 } when pt. has not achieved Euthyroid state
- 30% mortality – mostly due to Cardiac arrhythmias / Cardiac failure

Clinical features:

- Any person with thyrotoxicosis presenting with
 - Fever + Delirium
 - Seizures
 - Loss of consciousness

Management:

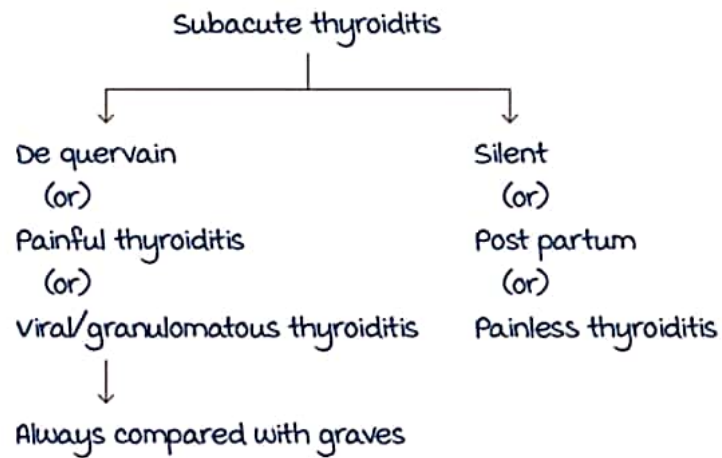
- Propyl thiouracil in Large doses:
 - 1000 mg stat
 - 250 mg every 4 hours
- Iodide given – as
 1. It produces Wolff – Chaikoff effect
 2. Inhibits proteolysis
 - Oral iodides like Iopanoic acid 500 mg can be used
- Steroids – hydrocortisone 100 mg Tds i.v
- Beta blocker – Propranolol 60 mg 4th hourly

Differential diagnosis of graves:

- Thyrotoxicosis without hyperthyroidism – Subacute thyroiditis

Acute thyroiditis

- In Acute thyroiditis, TFT is normal
- Seen in children
- Characterised by pain in the neck
- infectious etiology – Staph aureus – m.c
- Radiation or Trauma induced
- Focus of infection: Pueriform sinus



Dequervain / viral / granulomatous thyroiditis:

- Seen in woman - 80-50 yrs
- No single virus has been isolated
- Associated with HLA B - 35
- most often it is post viral
- Fever + painful thyroid / sore throat + Pain referred to ear + ESR $\uparrow\uparrow \Rightarrow$ Thyroiditis (most probably)
- Due to release of stored hormones $\rightarrow$ initially patient presents with symptoms of thyrotoxicosis followed by hypothyroidism & finally recovery
- Clinical course of subacute thyroiditis
 - 1-6 wks - Free $T_3/T_4 \uparrow\uparrow$
 - TSH $\downarrow$
 - 6-12 wks - Free $T_3/T_4 \downarrow$
 - TSH $\uparrow$
 - >12 wks - Recovery
- In I^{123} scintigraphy - Graves - B/L increased diffuse uptake
 - Subacute thyrotoxicosis - As the gland is not over working there will be decreased uptake

Treatment:

- Aspirin / NSAIDs - 600 mg 6th hourly
- If not responding - Steroids
- Permanent hypothyroidism can develop in 15% of patients (85% recover)

Painless thyroiditis / silent thyroiditis:

- Seen in post partum females
- most of them with underlying autoimmune illness (mc: Type 1D.m)
- Painless
- ESR - Normal
- Anti - TPO Ab - Positive
- Steroids have no role
- Spontaneous recovery
- β - blockers can be used
- High chance of recurrence in the subsequent pregnancy

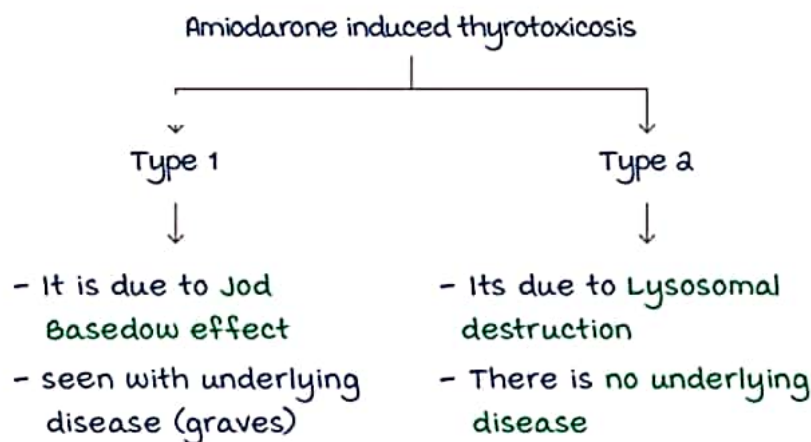
Chronic thyroiditis - Riedel's thyroiditis

- In chronic thyroiditis TFT is normal
- middle aged woman
- Painless thyroid with local symptoms
- Dense fibrosis
- Hard mass
- IgG₄ related disease
- Tru-cut biopsy is in 3 conditions:
 - Riedel's thyroiditis
 - Anaplastic ca
 - Lymphoma
- In other cases, USG-Guided FNAC

Effects of amiodarone

00:51:55

- Amiodarone contains 39% of Iodine / weight
- Class III Antiarrhythmic drug
- Amiodarone can produce both Hypo & Hyper thyroidism / thyrotoxicosis
- Amiodarone induced hypothyroidism is transient & it is due to Wolff Chaikoff effect. Don't stop Amiodarone, start low doses of L-thyroxine
- Amiodarone induced thyrotoxicosis is a serious condition



Treatment of amiodarone induced thyrotoxicosis:

- Stop amiodarone
- Sodium ipodate or trypanoate inhibit the release of hormones
- Perchlorates can be used - Na/I symport is Inhibited
- Steroids can also be used

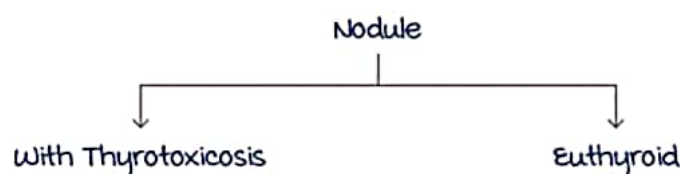
Low T_3 / sick euthyroid syndrome

00:55:36

- Seen in acutely ill patient under the effect of IL-6
- Seen in people who are fasting or chronic systemic illness
- Deiodinase is inhibited, $\rightarrow T_4$ is not converted to $T_3 \rightarrow$ low T_3
- All the excess T_4 is converted to $\uparrow rT_3$ (reverse T_3)
- There will be $\downarrow T_3$, $\uparrow T_4$, $\uparrow TSH$, $\uparrow rT_3$ - most common pattern
- If the patient is very ill, there can be $\downarrow T_3$ & $\downarrow T_4$, $\downarrow TSH$ its due to accelerated metabolism from muscle & liver due to reduced perfusion

Nodule

00:59:30



Nodule with euthyroid:

- In this the IOC is usg guided fnac or usg

usg features of malignancy:

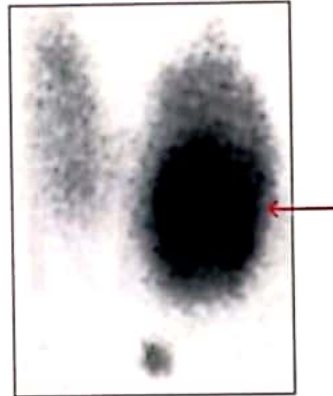
- Hypoechogenicity*
 - An absent halo
 - Irregular margins*
 - Taller than wide shape*
 - Presence of micro - calcifications*
 - Increased intranodular vascularity
 - Extra thyroidal extension
 - Nodal disease in neck
- No findings are definitive

Nodule with thyrotoxicosis:

- IOC thyroid scintigraphy - I^{123} scan

Hot nodule:

- >99% benign, <1% malignant
- Increased radionuclide concentration
- may function independent of thyroid-Pituitary axis feedback mechanism (autonomous nodules)



A solitary "toxic" nodule with suppression of the remainder of the thyroid

Cold nodule:

- Non-functioning thyroid Nodule
- Large majority are benign, 15-25% malignant



Pathological diagnosis confirmed a benign adenoma in the region of cold spot (arrows)

Toxic Autonomous Nodule (toxic adenoma)

History:

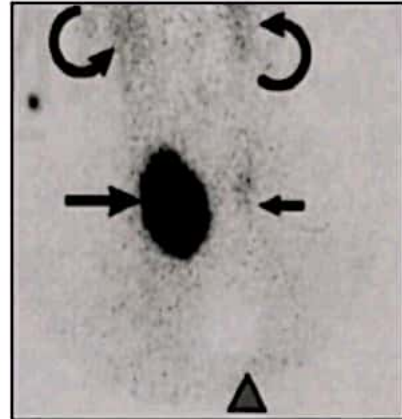
- 49-year-old woman

Labs:

- T4 = 15 ng/dl, TSH 0.4-4.5 IU/ml
- T3 = 304 ng/dl, FT4 0.7-1.6 IU/dl
- TSH < 0.01 IU/ml, FT6 230-430 ng/L
- The 24-hour RAIU was elevated (46%)

Scan

- Hot nodule occupies most or all of the right thyroid lobe with near-total suppression of the left lobe.
- The background activity is diminished to such an extent that the salivary glands are barely visualized



- A nodule with increased uptake and suppression of the remaining gland
- It is due to mutation in the TSH receptor signalling pathway
- It can be differentiated from Graves by scintigraphy. Here only some part will be uptaking the radionucleotide **Increased focal uptake**
- **Radio Iodine** is the treatment of choice

Toxic multinodular goitre

01:06:02

Toxic multinodular Goiter

History:

- 71-year-old man with anxiety and weight loss

Laboratory values:

- T4 = 121 ng/dL
- T3 = 299 ng/dL
- TSH < 0.01 IU/ml
- The RAIU was 17% at 6 hours and 37% at 24 hours

Scan:

- Enlarged thyroid with overall non uniform uptake
- Areas of both increased and decreased activity are scattered throughout the gland



- There will be areas of both increased and decreased uptake
- Toxic MNG, seen in elderly with features of thyrotoxicosis like AF, tremor, weight loss

INTRODUCTION TO MGE AND DIARRHOEA

Malabsorption

00:03:26

- Diminished absorption of
 - Carbohydrates
 - Fat
 - Protein
- Hallmark of malabsorption → Steatorrhea
 - ↓
 - Pale fat bulky malodorous stool
- 72 hr fecal fat test = $\geq 7g$ (steatorrhea)
 - (100 gm fat X 5 days
 - & testing fecal fat for
 - Last 3 days)

Diarrhoea

00:08:47

- Stool water content > 200 ml in 24 hrs
- most prominent clinical symptom of a patient with malabsorption – Diarrhoea
- Fat malabsorption
 - ↓
 - ↑↑ Osmotic load delivered to colon
 - ↓
 - Osmotic diarrhoea

BRISTOL STOOL CHART			
	Type 1	Separate hard lumps	Severe constipation
	Type 2	Lumpy and sausage like	mild constipation
	Type 3	A sausage shape with cracks in the surface	Normal
	Type 4	Like a smooth, soft sausage or snake	Normal
	Type 5	Soft blobs with clear-cut edges	Lacking fibre
	Type 6	mushy consistency with ragged edges	mild diarrhea
	Type 7	Liquid consistency with no solid pieces	Severe diarrhea

Active space

Osmotic diarrhoea v/s secretory diarrhoea

00:13:43

Secretory diarrhoea can be due to:

- Toxigenic : E. Coli, V. Cholera
- Tumors : VIP secreting tumor

	Osmotic diarrhoea	Secretory diarrhoea
I. Fasting	• Improvement with fasting	• No improvement with fasting
a. Stool osmolar gap	• $>50 \text{ mosm/kg}$	• $<25 \text{ mosm/kg}$
↓		
	$\left(\begin{array}{l} \text{measured osmolarity} \\ \text{of stool} \end{array} - \begin{array}{l} \text{Calculated osmolarity} \\ \text{of stool} \end{array} \right)$	

$$= 300 \text{ mosm/kg} - 2 \times (\text{stool Na}^+ + \text{K}^+)$$

(N): Stool osmolar gap $<25 \text{ mosm/kg}$

* Factitious diarrhoea – Reduced stool osmolality

Small intestinal v/s large intestinal diarrhoea

00:22:16

Small intestinal diarrhoea	Large intestinal diarrhoea
• TB-Ileum - Crohn's disease- Ileum - Toxigenic • Large volume with ↓ frequency • No blood, pus mucus • Steatorrhea • Abdominal pain and vomiting • Tenesmus absent urgency absent	• Ulcerative colitis, Rectum Colitis • Small volume with ↓ frequency • Blood, pus, mucus ⊕ ⊕ ⊕ • No steatorrhea • Less chances of abdominal pain and vomiting - Tenesmus often present urgency often present

Acute v/s chronic diarrhoea

00:27:24

- Acute diarrhoea → < 14 days
→ mostly due to infections
- Chronic diarrhoea → > 2 weeks

Organisms involved

00:29:07

- m/c/c for viral diarrhoea in children → Rotavirus
- m/c/c for viral diarrhoea in adults: Norovirus
- Severe ileitis resembling appendicitis: *Yersinia enterocolitis*
- Diarrhoea due to *Campylobacter jejuni* trigger Guillain Barre syndrome
↓
Large intestinal diarrhea
- Severe inflammatory diarrhea affecting all 4 layers
↓
Colitis → *Shigella Dysenteriae*
(10^3 organisms sufficient)
- Staph aureus
Bacillus cereus
Clostridium perfringes } Preformed toxin

Preformed toxin – Staphylococcus

00:33:59

- Incubation period: 1-6 hrs
- Pork, canned meat, custard
- Vomiting is the prominent symptom with abdominal cramps due to preformed toxins (vagal stimulation)
- Fever
Hypotension } Never seen
- Diarrhoea is rare
- No role of any antibiotics

Preformed toxin – bacillus cereus

00:35:53

- 2 forms of food poisoning:

Incubation time:

1-6 hrs



- Due to uncooked fried rice
- Preformed toxin
- Vomiting predominant

6-12 hrs



- Due to pudding, meat balls dried potato
- Toxin formed inside small intestine
- Diarrhea predominant

* Requires only conservative management

Enterotoxigenic pathogens

00:38:11

- Toxigenic diarrhoea / Small Intestinal diarrhoea / Secretory diarrhea (Acute)
- **m/c**: Enterotoxigenic E.coli (ETEC)

Vibrio cholera



Small intestinal diarrhea



- Large volume
- Dehydration
- No invasion of mucosal surface
- Intestinal fluid loss due to toxin

Cholera

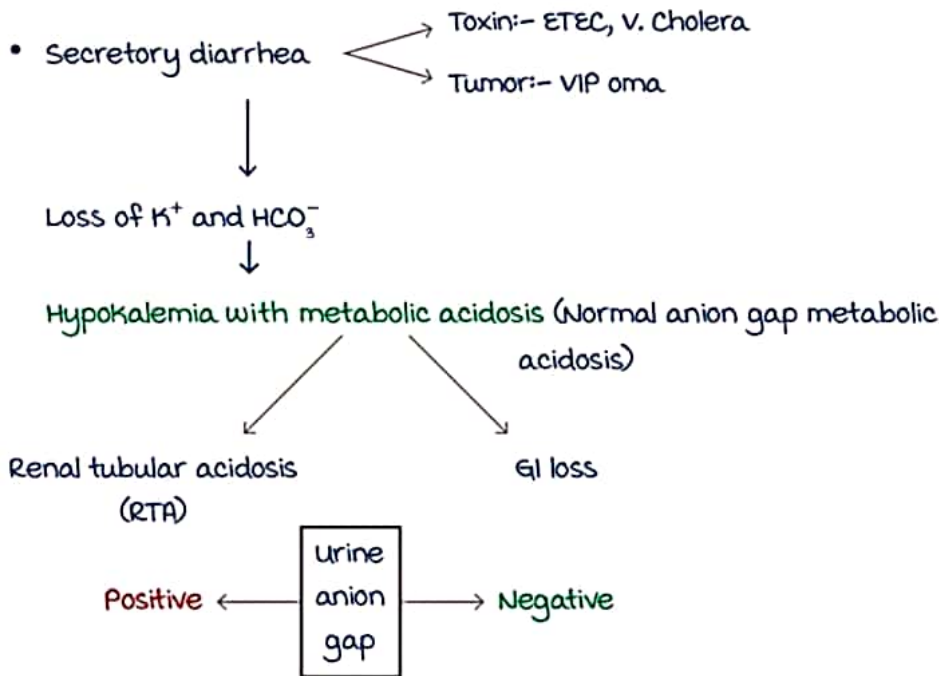
00:40:28

- Enterotoxin activates adenylyl cyclase → ↑cAMP



Responsible for toxigenic / Secretory diarrhea

- **Toxin Coregulated Pilus (TCP)** mediates attachment of vibrio to intestinal mucosa
- Inflammatory cells are **absent** in stool



- Ringer lactate is the fluid of choice in cholera
- DOC: Doxycycline
- DOC in pregnancy: Azithromycin

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

ETEC (Enterotoxigenic E.coli)

00:45:10

- m/c/c for :
 - I) Traveller's diarrhea
 - II) Community acquired diarrhea
 - III) Toxigenic diarrhea
- Produces heat labile toxin (LT toxin)

↓

Acts by increasing cyclic AMP
- EHEC (Enterohemorrhagic E.Coli) produces $O_{157} : H_7$ (Shiga like toxin)

↓

Hemolytic uremic syndrome

Causative organisms

00:54:26

- HUS → EHEC > Shigella dysenteriae
- Reactive arthritis → m/c worldwide : Chlamydia trachomatis
m/c India : Shigella dysenteriae
- Bone marrow suppression → Salmonella
- GBS → Campylobacter jejuni
- Toxic megacolon → Clostridium difficile
- Aortitis endovascular infection → NTS (Nontyphoidal Salmonellosis)
- Intestinal hemorrhage → Salmonella
- Right lower quadrant tenderness → Yersinia
- Small bowel lymphoproliferative disorder → Campylobacter

Incubation period

00:56:05

- 1 to 6 hrs : Staph aureus
B. cereus (vomiting) } Preformed toxin "heat stable"
- 8 to 16 hrs : B. cereus (diarrhea) → Toxin in GIT
Cl. Perfringens → Preformed } Heat labile
- > 16 hrs : All other organisms

Pseudomembranous enterocolitis

00:59:14

- Clostridium difficile related enterocolitis
- Antibody most implicated in pseudomembranous
- Colitis: Cephalosporins
Clindamycin
Amox / Ampicillin
Fluroquinolones
- Toxin A : Enterotoxin (small intestine)
- Toxin B : Cytotoxin (large intestine)

- Acute diarrheal disease with hemolysis following raw fish intake
- Kanamycin phenomenon on blood agar
- No role for antibiotics

Invasive colitis

00:48:31

- Small volume bloody diarrhea
- Abdominal cramps
- **Fecal leukocytes**
- Shigella / Salmonella / Yersinia / C. Jejuni / E. Histolytica
↓
m/c
- Stool with inflammatory exudate containing neutrophils, mucus and blood
- Invasion by **plasmid antigen**
- Shigella enterotoxin can produce toxigenic diarrhea
Invasive colitis – Plasmid mediated
- Shiga toxin → Cytotoxin → **HUS**
- Invasive diarrhea v/s UC
Fecal WBC → Infection
markers for UC in stool: **Fecal lactoferrin, calprotectin**
- Doc for shigella: **Ciprofloxacin**
- Non typhoid salmonellosis
↓
most dreaded complication: **Aortitis / Endovascular infection**
- **Perforation** is the commonest complication of enteric fever
- Diarrhoea is seen in **2nd week** of enteric fever

MALABSORPTION

Hallmark of malabsorption **steatorrhea**

Steatorrhea is $> 7g / 24$ hour fecal test

most prominent clinical manifestation is diarrhea

Basic physiology of absorption

00:01:03

Villi are for absorption

Crypts for secretion

Intestine has -

1] mucosa

- Epithelial cells
- Lamina propria
- muscularis mucosa

2] Submucosa

3] muscular layer

- Outer longitudinal
- Inner circular

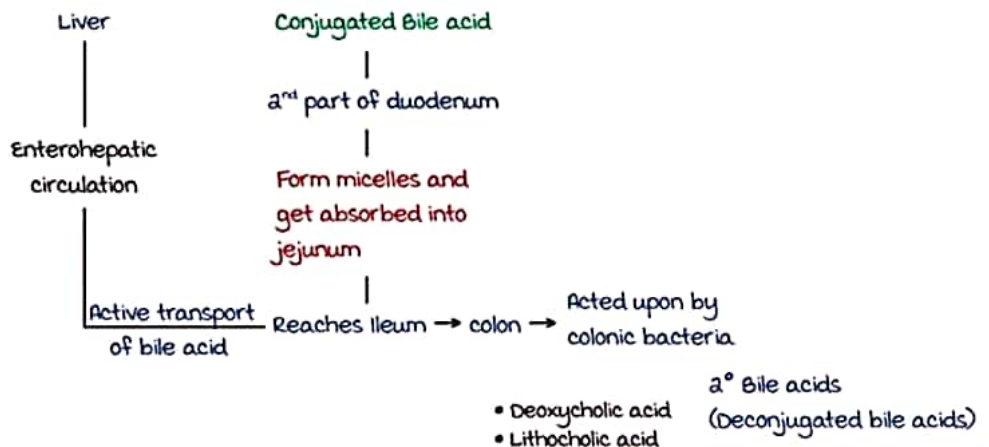
4] Serosa

- Continuous removal of intestinal epithelial cells occur every 48-72hrs
- Cylindrical structures surrounding villi are called **Crypts of Lieberkuhn**
- Alpha defensins, lysozymes, phospholipase A₂ are produced by Paneth cells
- Luminal surface of small intestine has visible mucosal folds called plica circularis
- Interstitial cells of Cajal are pacemaker cells of small intestine
- **Brunner's gland** are submucosal glands in duodenum which secrete bicarbonate rich alkaline juice
- macroscopic lymphoid aggregates in ileum - **Peyer's patches**

- Long chain fatty acids are predominantly absorbed in the jejunum

1 Bile acids

- Essential for micelle formation
- Formed in **cytoplasm of hepatocyte**
- 1° Bile acids
 - Cholic acid
 - Chenodeoxycholic acid
- 1° Bile acids are conjugated with **Glycine** & **Taurine** to form conjugated bile acids → **Bile salts**
- 500mg of bile acid is formed per day
- Rate limiting enzyme α hydroxylase
- Bile acid pool → 4g due to **Enterohepatic circulation**



- 500 mg formed per day
 - ↓
 - 500 mg excreted per day
 - ↓
 - Pool size 4g is maintained

Problems (hits)

I Bile acids

1] **Cirrhosis** No bile acid fat malabsorption

2] Bile duct

- Primary biliary cirrhosis (autoimmune destruction of intrahepatic bile duct)
- Primary sclerosing cholangitis [fibrosis of IHBD
EHBD]

3] small intestinal bacterial overgrowth

Lot of bacteria in small intestine ($\uparrow\uparrow$) deconjugate bile acid

Conjugated bile acid is needed for micelle formation leading to fat malabsorption

4] Ileal disease (Crohn's, TB)

Defective enterohepatic circulation

II. Pancreas

1] $\downarrow$ **Pancreatic lipase** (chronic pancreatitis) $\rightarrow$ ($\downarrow$) lipolysis



TG is not broken into
FA & glycerol

III. Intact small intestinal mucosa for absorption (jejunum)

Affected by

- 1] Celiac disease
- 2] Whipple disease
- 3] Tropical sprue

IV. Esterification and chylomicron formation

Affected by

- Abetalipoproteinemia

V. Delivery by lymphatics to tissues

Affected by - Intestinal lymphangiectasia

- If integrity of small intestinal mucosa is lost, all three absorptions are affected (fat, protein carbohydrate)

I. Short chain fatty acids (<8 carbon atoms)

- Not a part of diet
- Formed from unabsorbed carbohydrate in colon

II. medium chain fatty acids (8-12 carbon atoms)

- Only in small amount (eg. Coconut oil)
- Doesn't require lipolysis
- No need for micelle formation
- Completely absorbed in SI

III. Long chain fatty acids (>12 carbon atoms)

- Major protein in diet
- Requires lipolysis
- Requires micelle formation

Bile acid diarrhea v/s Fatty acid diarrhea

Bile acid diarrhea

Less (mild) ileal
disease where EHC is only
mildly affected
↓
Compensated by
increased bile synthesis
from liver
↓
No malabsorption
↓
Diarrhea due to ↑ bile
acid in colon
(Bile acid ↑ osmolality of
the stool)
↓
(No response to low fat
diet)

FA diarrhea

osmotic diarrhea due to
extensive ileal disease
↓
Ileal bile acid reabsorption is
defective
↓
Liver not compensating by
↑ bile acid synthesis
↓
No conjugated bile acids
↓
Defective fat absorption
↓
Steatorrhea, osmotic
diarrhea
↓
(Response to low fat diet)

mostly absorbed as monosaccharides in jejunum

disease affecting jejunal mucosal integrity will affect all 3 absorptions

- Glucose > galactose absorbed by → SGLT sodium dependent glucose transporter-1 (2° active transport)

(mutation) ↓

Familial glucose galactose malabsorption syndrome

- Fructose is absorbed by GLUT 5 [facilitated diffusion]
[SGLT 2 is present in PCT of kidney]

Lactose intolerance

00:38:36

Deficiency of lactase enzyme

Primary

- Severe
- From birth, diarrhea & failure to thrive

secondary

- Acquired
- 2° to infection
- IBS like symptoms ⊕

Diagnosed by

- stool reducing substance > 10%
- Stool acidic PH

Diagnosis of carbohydrate malabsorption

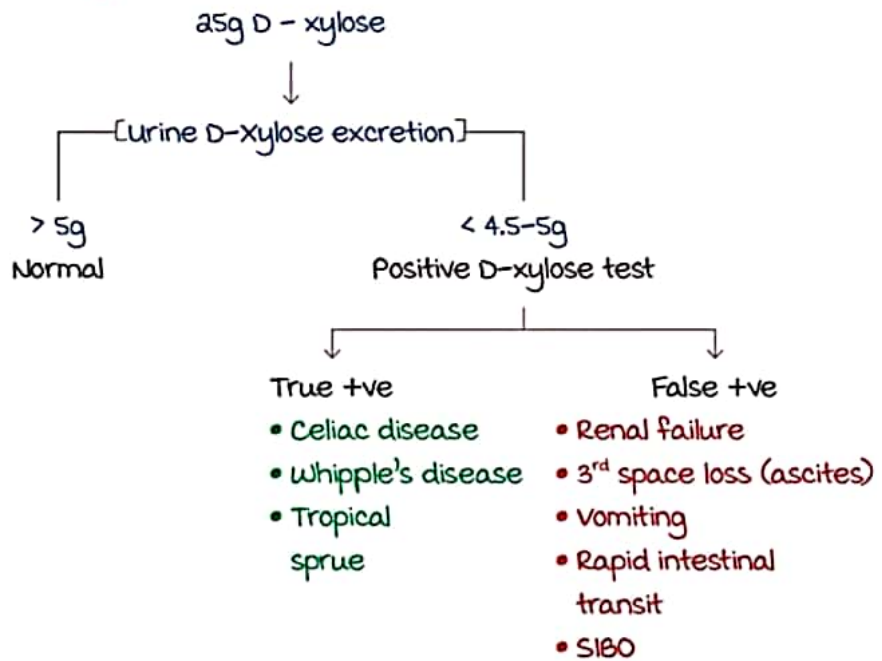
00:40:45

1. urine d-xylose test

- (Best non-invasive test for carbohydrate malabsorption)
(Best non-invasive test overall → 24 hr fecal fat test)
(Best non-invasive test for fat malabsorption)

xylose requires only an intact small intestinal mucosa for its absorption [∴ xylose is used]

urine D-xylose test



Protein malabsorption

00:45:24

Predominantly absorbed in jejunum as amino acids

I. Hartnup disease

Present with features of pellagra

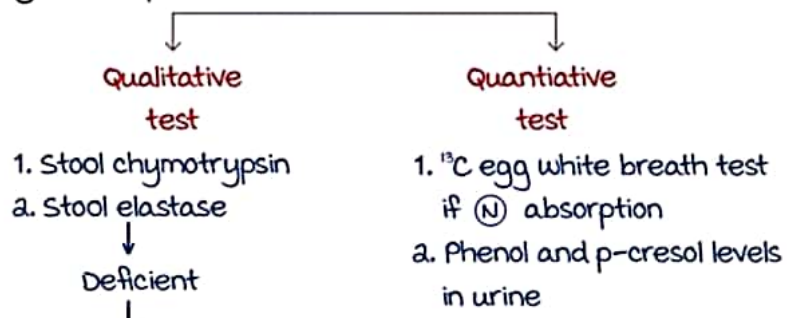
II. Enterokinase deficiency

Enterokinase is needed for activating trypsin

III. Cystinuria

Defective absorption of Cysteine / Ornithine / Lysine / Arginine

Diagnosis of protein malabsorption



Best → 72hr fecal fat

- Stool fat by sudan III stain (Qualitative test)
- Acid steatocrit test
- ^{14}C triolein breath test
- Lactose hydrogen breath test
 - Hydrogen in breath indicates carbohydrate malabsorption

[Gold standard for diagnosis of malabsorption - Small intestine mucosal biopsy]

Only 3 conditions are 100% diagnosed with diffuse specific findings

- 1) whipple
- 2) Abetalipoproteinemia
- 3) Agammaglobulinemia

Schilling test

Step 1 → 1000 μg of unlabelled vit B₁₂
(to saturate stores)



with (or) soon after 1 mg of radiolabelled vit B₁₂



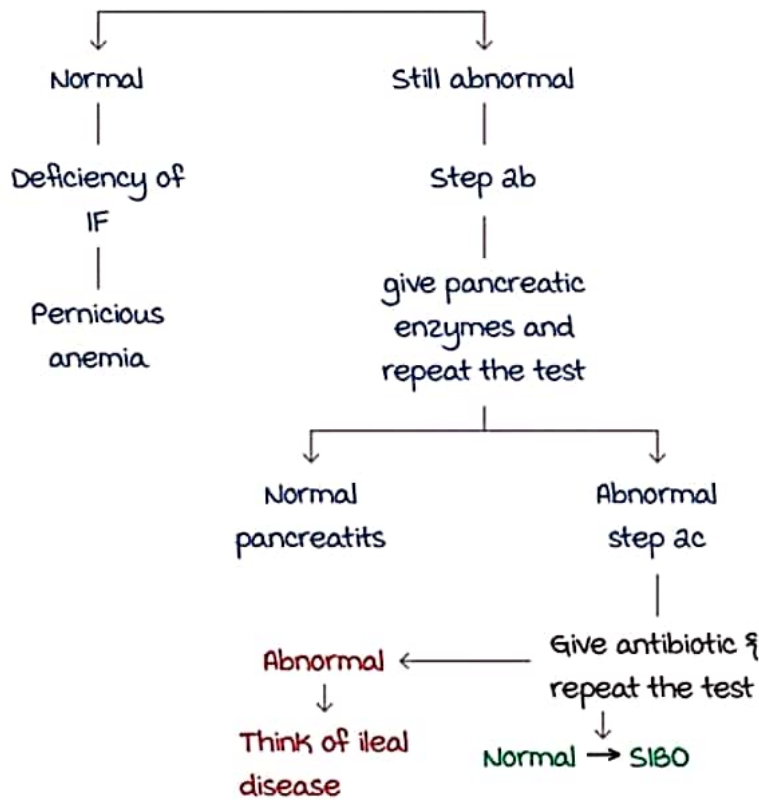
urinary excretion in 24 hrs



> 10% of radiolabelled vit B₁₂ (N)

< 7% → Positive → vit B₁₂ malabsorption

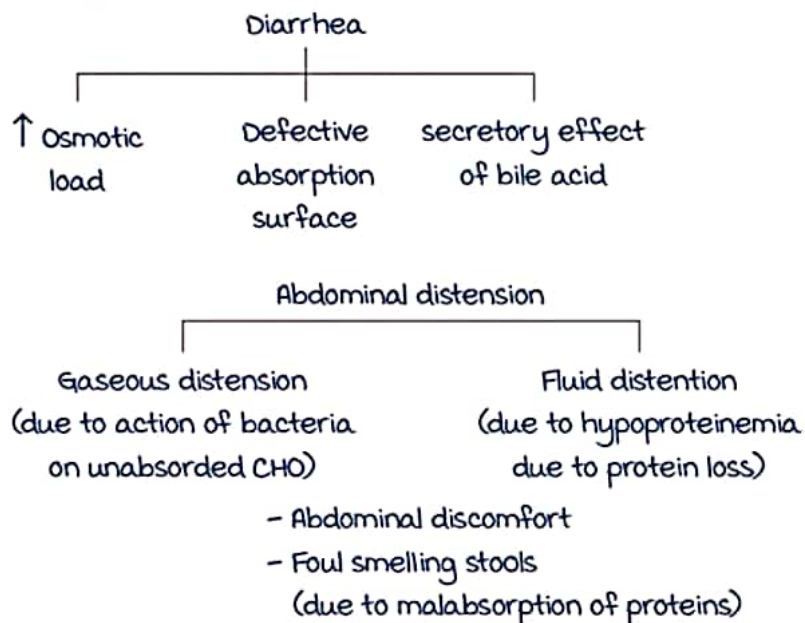
Step 2a → Give intrinsic factor and repeat the test



Symptoms of malabsorption

01:02:00

I. GI Symptoms



II. musculoskeletal symptoms

1. Bone pain
2. Osteomalacia → vit D deficiency
3. Fracture (#)

Clinical features

1. Acanthocytes on peripheral smear
2. Neurological features
3. 100% diagnosed by post prandial biopsy
4. Steatorrhea
5. Histology → vacuolation within enterocytes

Intestinal lymphangiectasia

01:17:10

- I. Congenital – multiple lymphatics involved
- II. Acquired – a° to infection

Present as protein losing enteropathy

- Hypoproteinemia
- Edema
- Fat malabsorption (steatorrhea)

Diagnosed by α_1 antitrypsin in stool

4. Tetany
5. Paraesthesia
6. muscle weakness → d/t deficiency of Ca, mg, P

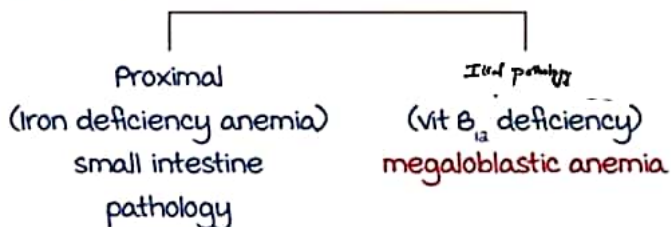
III. Cutaneous

1. Easy bruisability → d/t deficiency of vit K
2. Ecchymosis
3. Neuropathy } d/t deficiency of vit E
4. Ataxia }
5. Night blindness } d/t deficiency of vit A
6. Follicular hyperkeratosis }
7. Acrodermatitis enteropathica - d/t deficiency of Zinc
8. Hyperpigmented dermatitis - d/t deficiency of Niacin
9. Perifollicular haemorrhage - d/t deficiency of vit C

IV. miscellaneous

1. Weight loss + fatiguability + edema + ascites + muscle wasting + d/t loss of protein [DD - Nephrotic syndrome]

2. Anemia



3. Oxalate stones in kidney (Oxalate not chelated with Ca^{2+} as Ca^{2+} binds to fatty acid)
4. Peripheral neuropathy (d/t vit B₁₂ (or) E deficiency)

Abetalipoproteinemia

01:13:14

- Defect in fat absorption
- Defective chylomicron formation
- d/t absent β -lipoprotein (Apo B₄₈)
- ↓
- Hypolipidemia

Active space

CELIAC DISEASE, WHIPPLE'S DISEASE & TROPICAL SPRUE

Celiac Disease :

00:00:35

Also known as : Celiac sprue

Non - tropical sprue

Gluten sensitive enteropathy

It affects : Proximal small intestinal mucosa (Duodenum & jejunum)

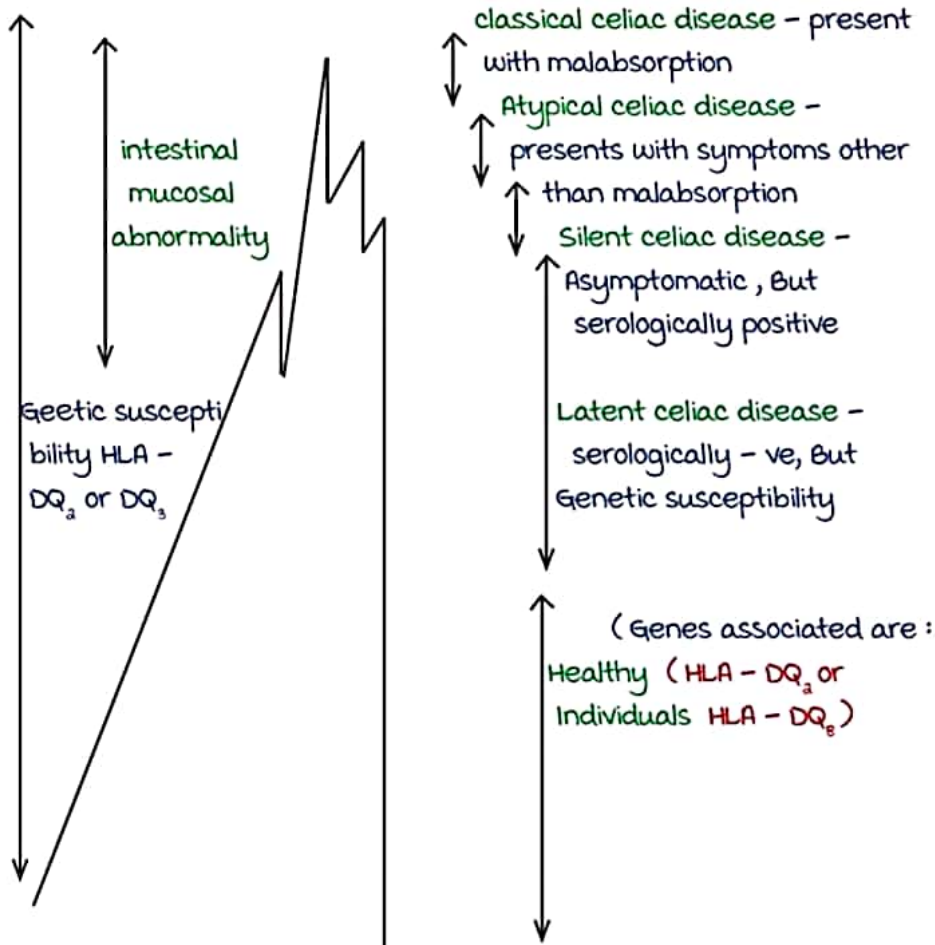
chief antigen : Gliadin

It is completely reversible within 6 months of gluten restriction
(Both clinically & histologically)

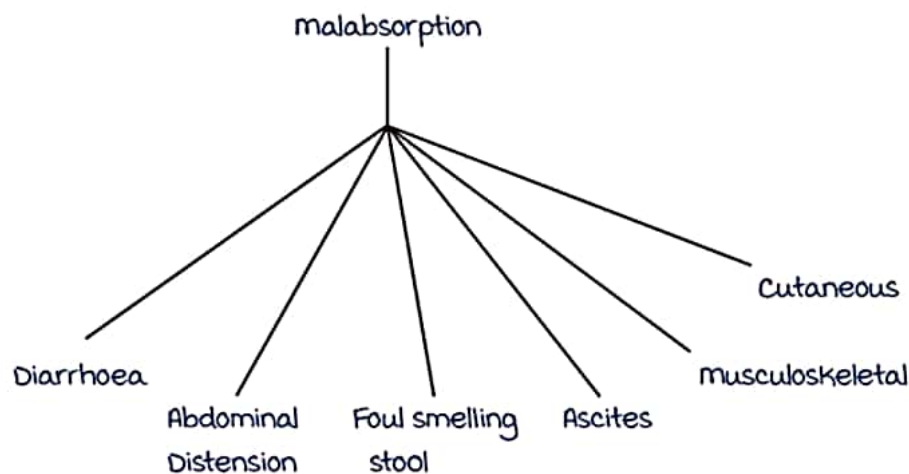


If not reversible → It is known as Refractory Celiac disease .

Celiac disease is also known as Iceberg disease



Signs of malabsorption :



Atypical celiac disease

00:06:41

Patients presents with symptoms other than malabsorption and can present at any age .

Atypical symptoms :

- a) Short stature & failure to thrive
- b) unexplained Fe deficiency anemia .
- c) unexplained Osteopenia .
- d) Ataxia & peripheral neuropathy due to vitamin-E
- e) associated with hyposplenism
- f) ↑ LFT

Diagnosis of celiac disease

00:08:23

Diagnosis is by biopsy & serology .

Biopsy Findings : (non - specific)

- 1) Findings localised to mucosa .
- 2) villous atrophy
- 3) Crypt hyperplasia .
- 4) mucosal thickness normal
- 5) Lamina propria infiltrates
- 6) vacuolar degeneration of surface epithelium may be seen

Serology :

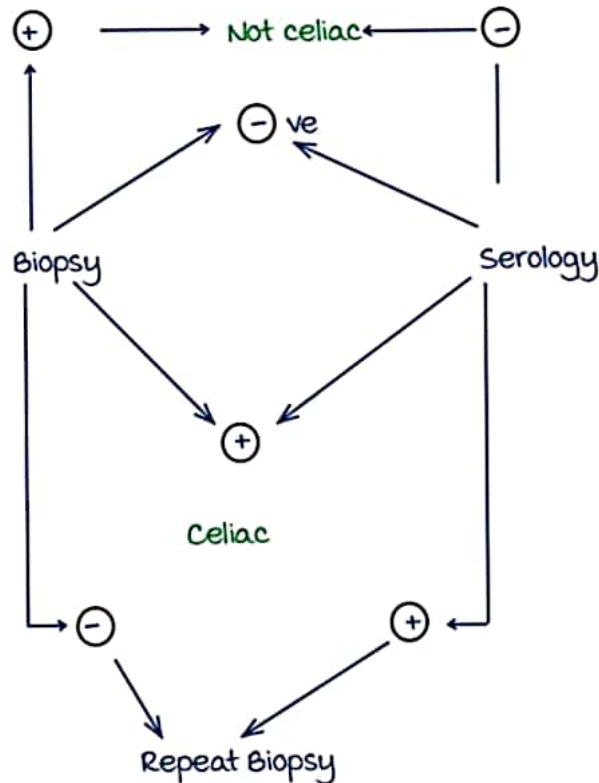
- 1) Antigliadin antibodies (IgG / IgA) - non sensitive
non specific not used now

2) Anti Endomysial antibodies (IgA)

- done by Indirect Immunofluorescence
- Best sensitivity & specificity
- Labour intensive & costly

3) Anti Tissue Transglutaminase antibody (IgA)

- done routinely
- done by ELISA.

**Disorders associated with celiac**

00:15:32

- 1) Dermatitis herpetiformis
- 2) Type 1 DM
- 3) IgA nephropathy
- 4) Bird fancier's lung
- 5) Down's syndrome
- 6) hypo or hyperthyroidism

Treatment of Celiac disease :

- Gluten restriction

↓
If not reversible within 6 months

↓
Refractory Celiac disease

↓
Treat - with steroids

3 Potential dangerous complication :

- Enteropathy associated T - cell lymphoma .
- Small intestinal adenocarcinoma .
- Esophageal Squamous cell carcinoma .

Can eat : rice, Corn , maize , potato , soyabean .

Must not eat : wheat , Barley , Rye , oats

Whipple's Disease

00:19:23

Chronic multi system disease :

Involves : Small intestine - involves (Proximal + distal)

CNS

CVS

Joints .

It involves a Gram positive Actinobacteria .

- Tropheryma whipplei

↓
Can't be cultured , Slow doubling time

male > Females

more common in 50 -60 yrs of age

associated with HLA DRB1 13 , HLA DQ B1 06

1) Small intestine → malabsorption (Distal > proximal)

↓
vit B₁₂ deficiency

→ Lymphadenopathy

2) CNS involvement

- more Common in relapse
- CNS involvement in relapse - Bad prognosis
- m/c finding - Dementia (progressive)
and m/c finding - Progressive Supranuclear palsy
- Opsoclonus myoclonus
- myorhythmias (Occulo - masticatory
Occulo - facial)

3) CVS

- 2nd m/c of culture negative endocarditis
- mc cause of Culture negative endocarditis - HACEK

1st common CVS involvement in Whipple - endocarditis (mitral)

↓
myocarditis

4) Joints :

- Small Joints migratory intermittent polyarthrititis

Diagnosis of Whipple's

00:28:02

- Upper GI endoscopy with Small intestinal mucosal biopsy
- It Shows gram positive organisms which are PAS positive inside macrophages in lamina propria
- PCR assay to detect T. Whipple

Treatment of Whipple :

Induction : Ceftriaxone
or + Streptomycin } x 14 days
Penicillin G

Maintenance : Cotrimoxazole
(to prevent relapse) (cotrimoxazole used due to its good CNS penetration)

Tropical sprue

00:30:21

m/c Cause of malabsorption in India

- Panintestinal involvement
- Toxigenic coliform organisms are involved
Like Ecoli
Klebsiella
Enterobacter

- Presents with features of malabsorption

+ vit B12 deficiency

↓
(Hyperpigmentation of hands)

- Biopsy is similar to Celiac disease .

- In Celiac disease - Biopsy ⊕ but serology negative
↓
could be tropical sprue
- Treatment : Folic acid + Tetracycline .

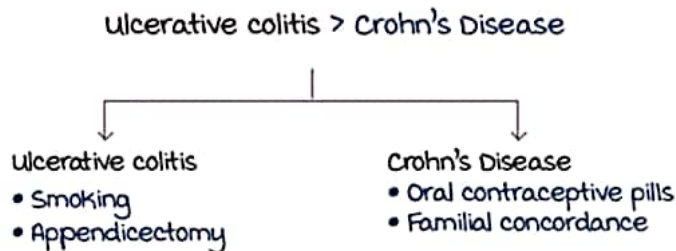
INFLAMMATORY BOWEL DISEASE

- It includes four Entities
 - 1) Ulcerative colitis
 - 2) Crohn's Disease
 - 3) microscopic colitis
 - 4) Diversion colitis
- Behcet's disease in rheumatology behaves as Crohn's Disease

Inflammatory bowel disease

00:01:36

- most commonly affects Jewish
- Least commonly affects Asians
- Occurrence Crohn's Disease > ulcerative colitis
- more common in males > females
- usually at 15-30yr Age - 1st episode starts
- Some cases diagnosed at 70 - 90 yrs
- Always characterized by remissions and relapses
- In females



Note : Smoking & Appendectomy are protective factors for UC

Causative factor for Crohn's Disease:

- Smoking
- Antibiotic use within 1st one year of life increases the risk of IBD by 3 times
- α - methyl Dopa use associated with occurrence of ulcerative colitis

Active space

TABLE	EPIDEMIOLOGY OF IBD	
	Ulcerative colitis	Crohn's Disease
Incidence (North America) per person-years	0-19.2 per 100,000	0 - 20.2 per 100,000
Age of onset	second to fourth decades and seventh to ninth decades	second to fourth decades and seventh to ninth decades
Ethnicity	Jewish > non-Jewish > African American > White, Hispanic > Asian	
Female/male ratio	0.51-1.58	0.34-1.65
Smoking	may prevent disease (odds ratio 0.58)	may cause disease (odds ratio 1.76)
Oral contraceptives	No increased risk	Odds ratio 1.4
Appendectomy	Protective (risk reduction of 13-26%)	Not protective
monozygotic twins	6-18% concordance	38-58% concordance
Dizygotic twins	0-2% concordance	4% concordance
Antibiotic use in the first year of life	2.9 x the risk of developing childhood IBD	

Genetic disorders associated with IBD

00:08:15

1) Turner's syndrome

- Both ulcerative colitis and Crohn's disease

2) Hermansky pudlak syndrome - Autosomal Recessive

- a) Granulomatous colitis
- b) Platelet functional defects
- c) Occulo-cutaneous albinism
- d) Pulmonary fibrosis

3) Glycogen storage disease type 1 (von Gierke's Disease)

4) Wiskott-Aldrich Syndrome

- Due to WASP gene mutation on X - Chromosome
- Recurrent eczema

5) IPEX syndrome - Immunodysregulation Polyendocrinopathy Enteropathy X-linked

- Loss of Fox P₃

- Fox P₃ → Transcription regulating factor



Cell - mediated immunity
which mediates tolerance

- T- regulatory cells identified by

CD3 → Pan T- cell marker

CD4 → T - helper cell marker

CD25 → T- regulatory cell

- T- regulatory cells have an antigen → Fox P₃

Loss of Fox P₃



Loss of T- regulatory cells



Autoimmune inflammation

- It includes

ulcerative colitis

Type 1 Diabetes mellitus

Dermatitis

- most powerful antiinflammatory cytokine → IL-10

- Deficient IL-10 → Early onset refractory IBD

Active space

TABLE Primary genetic disorders associated with IBD		
Name	Genetic Association	Phenotype
Turners syndrome	Loss of part or all of X Chromosome	Associated with UC and colonic CD
Hermansky-Pudlak	Autosomal recessive Chromosome 10q23	Granulomatous colitis, oculocutaneous albinism, Platelet dysfunction, Pulmonary fibrosis
Wiskott Aldrich Syndrome (WAS)	X-linked recessive disorder, loss of WAS protein function	colitis immunodeficiency, Severely dysfunctional Platelets, and thrombocytopenia
Glycogen storage disease	Deficiency of the Glucose-6-phosphate transport protein type B1	Granulomatous colitis, presents in infancy with hypoglycemia, growth failure, hepatomegaly, and Neutropenia
Immune dysregulation Polyendocrinopathy Enteropathy X-linked (IPEX)	loss of FoxP3 transcription factor and T regulatory cell function	UC like autoimmune enteropathy, with endocrinopathy (neonatal type 1 diabetes or thyroiditis), dermatitis
Early onset IBD	Deficient IL - 10 and IL - 10 receptor function	Severe, refractory IBD in early life

Etiopathogenesis of IBD

00:15:41

Crohn's Disease:

- Genetically Susceptible individuals
- NOD-2 gene on chromosome 16-mutation**

1) Defective clearance of intracellular bacteria

mycobacterium paratuberculosis

- Our innate immune system easily clears mycobacterium paratuberculosis
- This explains the association of mycobacterium paratuberculosis with **Crohn's disease**

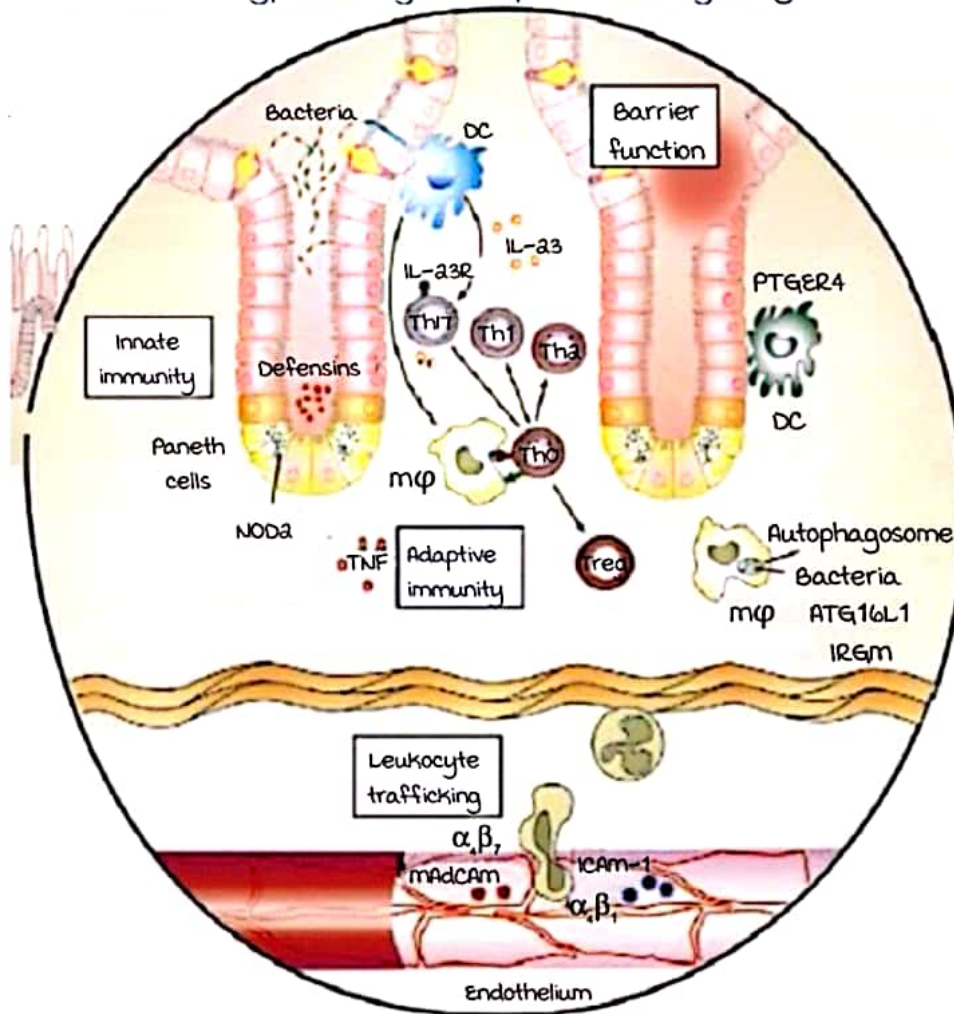
2) Paneth cells are defective:

- Paneth cells are responsible for defence
- They secrete Lysosome, Proteases etc.,
- So, innate Immunity is not acting

Resulting in hyperactivity of adaptive immunity (Th₁ response)

3) Defective Autophagy:

Also results in hyperactivity of adaptive immunity along



Ulcerative colitis

00:21:12

- 50% → rectal involvement → Proctitis
- 30-40% → Rectum
+ sigmoid colon } → Proctocolitis

- 10-20% → Complete colon → Pancolitis
- Of these 10% cases of pancolitis have ileal involvement
↓
Backwash ileitis
- 'Continuous' involvement

Gross features of ulcerative colitis

00:24:17

- 1) Superficial inflammation of mucosa and submucosa
- 2) 1st change → Erythematous mucosa with fine granular surface
- 3) Hemorrhage, edema, ulceration of mucosa
↓
Inflammatory polyps due to epithelial regeneration
↓
Pseudo polyps
- 4) Atrophic featureless, short and narrow colon
↓
Lead pipe or pipestem colon
With no haustrations



FIGURE Ulcerative colitis. Diffuse (nonsegmental) mucosal disease, with broad areas of ulceration. The bowel wall is not thickened, and there is no cobblestoning.



FIGURE Crohn's disease of the colon showing thickening of the wall, with stenosis, linear serpiginous ulcers and cobblestoning of the mucosa.

Radiology:



Lead pipe colon - rigid, ahastral appearance of colon - Chronic ulcerative colitis

Lead pipe sign - describes the rigid and featureless appearance of the colon in chronic ulcerative colitis. The sign is due to a complete loss of haustral markings and usually a degree of uniform luminal narrowing due to chronic bowel wall thickening.

microscopic features:

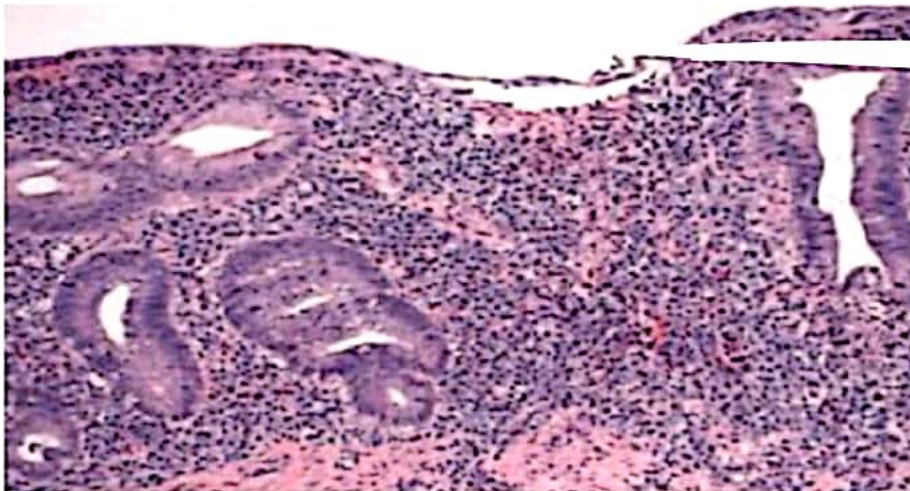


FIGURE medium-power view of colonic mucosa in ulcerative colitis showing diffuse mixed inflammation, basal lymphoplasmacytosis. Crypt atrophy and irregularity, and superficial erosion these features are typical of chronic active ulcerative colitis.

- Superficial inflammation – mucosa/submucosa
- Loss of crypt architecture
- Cryptitis – non-specific
- Basal plasma cells and lymphoid aggregates
- Paneth cell metaplasia

Crohn's disease

00:29:52

- Can involve any part of GIT
- Characterised by skip lesions
- Transmural involvement
- 30–40% has ileitis
- 40–50% has ileocolitis
- 15–20% has colitis
- most common pattern –

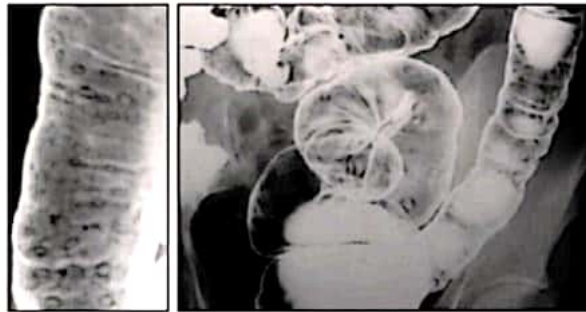
Macroscopy of Crohn's disease

00:31:39

- Segmental involvement with skip lesions
- Earliest findings are Aphthous ulcers

Aphthoid ulcers (target sign)

- Pathology: mucosal ulcers with surrounding translucent mound of edema



- Linear serpiginous ulcers
- Stellate ulcers will fuse longitudinally & transversely to leave behind areas of uninvolved mucosa



Cobble – stone appearance

Cobble stoning
in CROHN'S



- major complications

a) Thickening of bowel wall and fissures, fistula and abscess



which will lead to strictures & fibrosis



Garden hose or hose pipe appearance

b) Thickened mesentery encasing bowel wall



Creeping mesenteric fat

Microscopy of Crohn's disease

00:37:12

1) Transmural involvement

2) Non Caseating granuloma seen in any layer or uninvolved bowel or extraintestinal

3) mesenteric adenopathy

4) Pyeloric metaplasia

5) Lymphoid aggregates

6) Cryptitis

Clinical features of ulcerative colitis

00:39:34

Proctitis: fresh bleeding per rectum

Or

Blood streaked on to the surface of hard stool

Proctocolitis:

Large bowel diarrhoea



Small volume frequent stools with blood,
Pus, mucus and Tenesmus

Pancolitis

- Clinical examination is almost normal
 - Systemic Symptoms like fever, weight loss rarely
 - velvety edematous rectal mucosa
 - 90% cases have relapsing course
 - Fecal lactoferrin
 - Fecal calprotectin
- } Elevated in ulcerative colitis

- Symmetrical and continuous inflammation
- Erythematous mucosa with decreased vascularity
- Hemorrhage and ulcers in mucosa
- Inflammatory pseudopolyps
- Loss of haustrations, shortening & narrowing of colon



Lead pipe or pipestem appearance

Endoscopic criteria for mayo score				
	0	1 point	2 points	3 points
N o r m a l		mild erythema ↓ vascularity mild friability	moderate marked erythema lack vascular pattern friability	severe spontaneous bleeding ulceration
				

Pseudopolyps in
ulcerative colitis



Radiology of ulcerative colitis

00:45:23

- Fine mucosal granularities
- Serrations producing hazy margins
- Superficial ulcers



Deep ulcers

Collar button ulcer

or

Collar stud ulcer



- Loss of haustrations, short and narrow colon



LEAD PIPE

or

PIPESTEM Appearance



Lead pipe sign - describes the rigid and featureless appearance of the colon in chronic ulcerative colitis. The sign is due to a complete loss of haustral markings and usually a degree of uniform luminal narrowing due to chronic bowel wall thickening

- Ileocolitis along with systemic symptoms (Low grade fever, weight loss)
- Due to presence of systemic symptoms, most often this disease diagnosis is confused with Tuberculosis
- Episodes of right lower quadrant pain relieved by diarrhoea
- more of small intestinal diarrhoea
- Features of malabsorption – no bile acid absorption
enterohepatic circulation is defective
- main complication in Crohn's Disease
↓
Due to Thickening of Bowel wall
 - 1) Obstruction
 - 2) Stricture
 - 3) Fissure
 - 4) Abscess
 - 5) Fistula → Extravesical
Perianal
- On Abdominal examination
Inflammatory mass palpable

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Endoscopy & Radiology - Crohn's disease

00:51:27

Endoscopy:

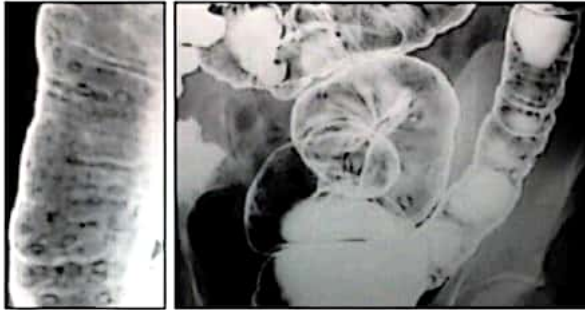
- Aphthous ulcers
- Cobble stone appearance
- Fissure, fistula and fibrosis etc

Radiology :

- 1st finding – Aphthous ulcers – Target sign

Aphthoid ulcers (target sign)

- Pathology: mucosal ulcers with surrounding translucent mound of edema



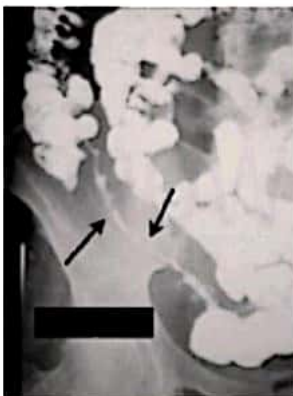
- 2nd finding – Fissure ulcers – Rose thorn appearance

Fissure ulcers (Rose thorn appearance)

- Pathology: Transmural ulcers



- String sign



Based on Degree of severity of Disease (ulcerative colitis)

Truelove and Wits classification of the severity of ulcerative colitis

mild
<4 stools/day, without or with only small amount of blood No fever No tachycardia mild anemia ESR<30mm/hr
moderate
Intermediate between mild and severe
Severe
>6 stools/day, with blood Fever>37.5°C Heart rate>90 beats/min Anemia with hemoglobin level<75% of normal ESR>39 mm/hr

ESR - erythrocyte sedimentation rate

Severe ulcerative colitis:

- Fever
- Tachycardia
- Anemia
- ↑ ESR
- >6 Bloody stools

Crohn's Disease

Stage	Characteristics
mild to moderate Crohn's Disease	People with mild to moderate Crohn's are able to eat food normally without dehydration, fevers, Stomach pain, blockages in their intestine, or Losing more than 10% of their body weight
moderate to severe Crohn's Disease	People are considered to have moderate to severe Crohn's if they do not respond to treatment for mild to moderate Crohn's or if they have high fever, significant weight loss, stomach pain or tenderness, occasional Nausea or vomiting or significant anemia
Severe crohns disease	People with severe crohns have symptoms despite taking steroids, or they have high fevers, persistent vomiting, blockages in their intestine, or an abscess

Severe Crohn's Disease

- Symptoms despite taking steroids
- Fever, vomiting, obstruction and abscess

Extra intestinal manifestations – IBD

00:56:06

- Always more common in Crohn's disease than ulcerative colitis
- With two exception which is more common in ulcerative colitis
 - 1) Pyoderma gangrenosum
 - 2) Primary Sclerosing cholangitis(PSC)
 - $\frac{2}{3}$ rd patients of PSC will have ulcerative colitis
 - But 5% with ulcerative colitis will have PSC

I SKIN:

Erythema nodosum

Pyoderma gangrenosum

II Ocular:

Episcleritis

Uveitis

III Arthritis:

Ankylosing Spondylitis

Large joint migratory Asymmetric PolyArthritis (LmAP)

IV stones:

Gall stones

Renal stones

V) Thromboembolism:

Dangerous complication

- Extraintestinal manifestation which correlate with relapse

In IBD

- Erythema Nodosum
- Episcleritis
- LMAP

Serology – IBD

01:00:51

In Crohn's Disease:

1) ASCA

- Anti - *Sacharomyces cerevisiae* Antibody
- used for screening
- Linked to early complication in Crohn's Disease
- Also positive in bechcet's disease

2) OMP - C

- Outer membrane Protein

3) APB

- Anti - pancreatic Antibody

4) Anti flagellin

5) Anti I_a → Correlates with risk for surgery

In ulcerative colitis:

1) P-ANCA → levels correlate with relapse

2) Antigoblet cell Antibody



Pyoderma
gangrenosum



Erythema
nodosum

Treatment of ulcerative colitis

01:04:02

5-Amino-salicylic Acid – **mainstay of treatment** is sulfasalazine

- It is a combination of
5- Amino Salicylic Acid + Sulfapyridine
(Active moiety) (Carrier molecule)
- 5-Amino-salicylic Acid gets absorbed in small intestine before it reaches the disease site (colon)
- To prevent its absorption, it is clubbed with the carrier molecule Sulfapyridine
- But because of complications **due to sulfa molecule** so, not used now
- **Delayed release 5-Amino-salicylic Acid** are used now
↓
mesalamine (Oral & Topical)

Induction Therapy:

1) mild ulcerative colitis

5-Amino-salicylic Acid (Topical or oral)

2) moderate ulcerative colitis

5-Aminosalicylic Acid

+

Steroids

Steroid refractory cases – Azathioprine or 6-mercaptopurine

3) Severe ulcerative colitis

IV steroids

+

IV cyclosporine or infliximab

Induction therapy for ulcerative colitis based on disease severity

mild disease
5-Aminosalicylates Topical (distal colitis) Oral (distal/extensive colitis) Combination
moderate disease
5-Aminosalicylates Topical (distal colitis) Oral (distal/extensive colitis) Combination Glucocorticoids Topical (distal colitis) Oral (distal/extensive colitis) Combination Azathioprine or 6-mercaptopurine
Severe disease
IV Glucocorticoids IV cyclosporine IV infliximab

TABLE Oral 5-ASA Preparations			
Preparation	Formulation	Delivery	Dosing
Delayed-release			
mesalamine (400, 800 mg) (Delzicol, Asacol HD)	Eudragit S (pH 7)	Distal ileum-colon	2.4-4.8 g 1.6-4.8 g
mesalamine (1.2 g) (Lialda)	mmx mesalamine (SPD476)	ileum-colon	2.4-4.8 g
Controlled-release			
mesalamine (250, 500, 1000 mg) (Pentasa)	Ethylcellulose microgranules	Stomach-colon	2-4 g (a. 1.5-4
Delayed - and Extended - release			
mesalamine (0.375 g) (Apriso)	Intelicor extended-release mechanism	Ileum-colon	1.5 g (ma.

maintenance Therapy

1) mild ulcerative colitis:

5-Aminosalicylic Acid
alone

2) moderate ulcerative colitis:

5-Aminosalicylic Acid
+
Azathioprine
Or
6-mercaptopurine

3) severe ulcerative colitis:

5-Amino salicylic Acid
+
Azathioprine
+
Infliximab

Table: Indications for surgery in patients with ulcerative colitis

Colonic dysplasia or carcinoma
Colonic hemorrhage, uncontrollable
Colonic perforation
Growth retardation
Intolerable or unacceptable side effects of medical therapy
medically refractory disease
Systemic complications that are recurrent or unmanageable
Toxic megacolon

Surgery in ulcerative colitis:

Total proctocolectomy with ileo-anal anastomosis

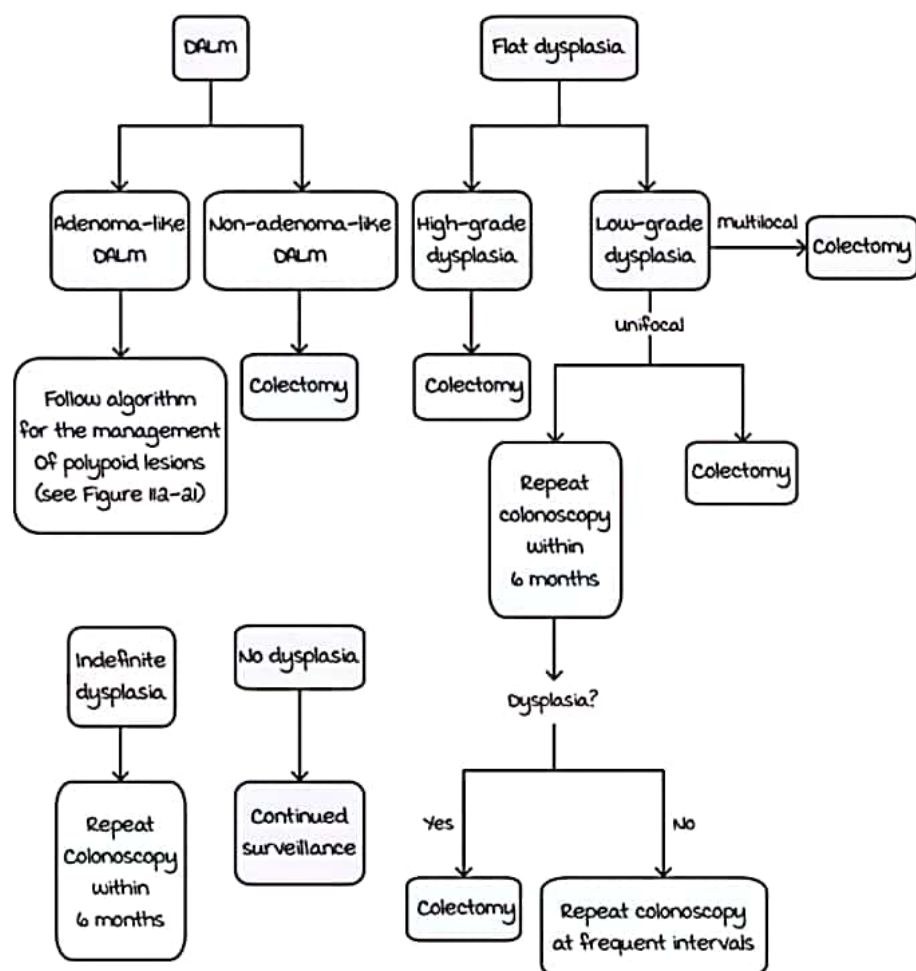
- If ulcerative colitis associated with primary sclerosing cholangitis, cholangiocarcinoma can occur
- Risk of cholangiocarcinoma persists even after colectomy

On Biopsy:

Two Possibilities:

1) Dysplasia Associated lesion or mass (DALM)

2) Flat Dysplasia



* ideal frequency has not been determined

Treatment of Crohn's disease

01:12:58

1) mild Disease:

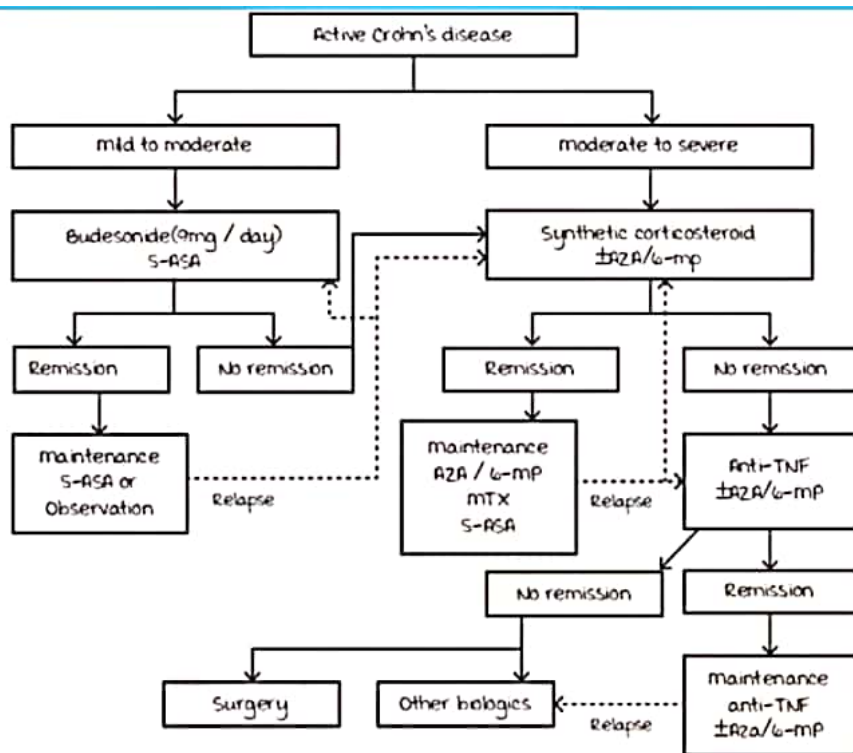
Oral budesonide 9mg /day
+
5-Aminosalicylic acid (5-ASA)

- maintenance with 5-ASA
- Oral budesonide is delayed released preparation
So, percentage of active drug in the blood is very less
No steroid related side effects or very less

2) moderate to severe disease:

Steroid (Oral or i.v)
+
Azathioprine or 6-mercaptopurine

- If remission achieved, then maintain with
Azathioprine or 6-mercaptopurine
+
Low dose methotrexate
- If remission not achieved
Start Anti-TNF- α
↓
If remission achieved
↓
maintain with Azathioprine + Anti-TNF- α
- monoclonal antibody approved against α_4 integrin
↓
Natalizumab
- Antibiotics are always given in Crohn's disease
- Crohn's disease has risk of carcinoma colon
- Also has risk of Leukemia /Lymphoma
- Carcinoma colon risk is more in ulcerative colitis than Crohn's disease



Important tables

01:18:32

Different clinical, Endoscopic, and Radiographic

	Ulcerative colitis	Crohn's disease
Clinical		
Gross blood in Stool	Yes	Occasionally
mucus	Yes	Occasionally
Systemic symptoms	Occasionally	Frequently
Pain	Occasionally	Frequently
Abdominal mass	Rarely	Yes
Significant perineal disease	No	Frequently
Fistulas	No	Yes
Small intestinal Obstruction	No	Frequently
Colonic obstruction	Rarely	frequently
Response to antibiotics	No	Yes
Recurrence after surgery	No	Yes
ANCA-positive	Frequently	Rarely
ASCA-positive	Rarely	Frequently

Endoscopic		
Rectal soaring	Rarely	Frequently
Continuous disease	Yes	Occasionally
Cobblestoning	Yes	Frequently
Granuloma on biopsy	No	Occasionally
Radiographic		
Small bowel significantly abnormal	No	Yes
Abnormal terminal ileum	No	Yes
Segmental colitis	No	Yes
Asymmetric colitis	NO	Yes
Stricture	Occasionally	Frequently

Differentiating crohn's colitis from ulcerative colitis:

FEATURE	CROHN'S COLITIS	ULCERATIVE COLITIS
Mucosal lesion	Aphthous ulcer are Common in early disease, late disease is notable for stellate, rake, bear claw, linear, or serpiginous ulcers and cobblestoning	micro ulcer are more Common, but larger ulcers are possible Pseudo polyps are more common
Distribution	Often discontinuous and asymmetrical with skipped segment of normal intervening mucosa, especially in early disease	Continuous, symmetrical and diffuse, with granularity or ulceration found in entire involved segments; however, periappendiceal inflammation (cecal patch) is common, even when the cecum is not involved
Rectum	Complete, or more often relative, rectal sparing	Typically involved with proximal distribution
Ileum	Often involved (approximately 75% of case)	Not involved except as backwash ileitis in Pan ulcerative colitis

Depth of Inflammation	mucosal, submucosal, and transmural	mucosal, transmural only in fulminant disease
Serosal findings	marked erythema and creeping fat (the latter is virtually pathognomonic)	Absent except in severe colitis or toxic megacolon
Perianal complications	Often prominent including large and skin tags, deep fissure, perianal fistula, that are often complex	Not prominent (fissure or fistula if present should be uncomplicated)
Strictures	often present	Rarely present suggest adenocarcinoma
Fistulas	Perianal enterocutaneous, rectovaginal enterovesicular and other fistula may be present	Absent except for rare occurrence of rectovaginal or perianal fistula
Histopathology	Granulomas are present in 15%-60% of patient (higher frequency in surgical specimens than in mucosal punch biopsies)	Granulomas should not be present (microgranulomas may be associated with ruptured crypt abscess)
	crypt abscesses may be present	crypt abscesses and ulcers are the defining lesion
	Focally enhanced inflammation often on a normal background is the hallmark	Ulceration on a background of inflamed mucosa
Serology	pANCA in 20%-25% ASCA in 41%-76%	pANCA in 60%-65% ASCA in 5%

SHORT BOWEL SYNDROME AND SIBO

Short bowel syndrome

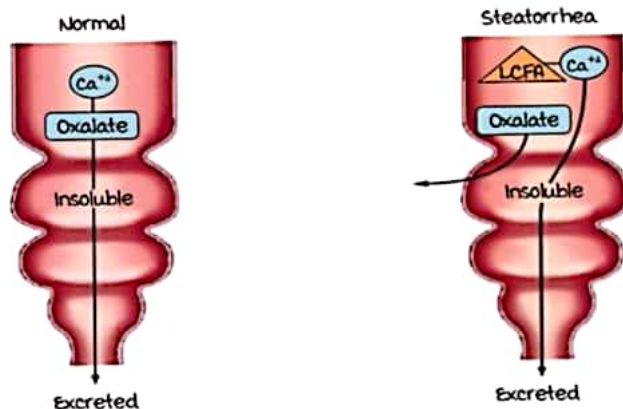
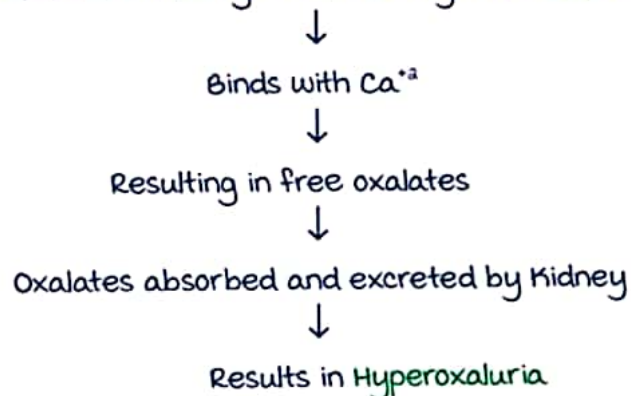
00:0029

- Due to resection of varying lengths of Intestine
- Which results in malabsorption
- most common cause in children is Necrotising Enterocolitis
- In Adults is
 - 1) mesenteric vascular disease
 - 2) Crohn's disease
- manifestation depends on the part of small intestine that is removed

Classical features

1) Hyperoxaluria:

- Unabsorbed Long - Chain Fatty Acids (LCFA)



Active space

a) cholesterol gall stones:

- Seen in ileal resection
- which is usually done in Crohn's disease tuberculosis
- Defective bile acid absorption



- Results in defective entero hepatic circulation



- Formation of cholesterol gall stones

3) D-Lactic Acidosis

- Normally, D-lactate is not formed in the body
- Due to Presence of unabsorbed carbohydrates and proteins in colon



Decreases the colonic pH



Changes the Bacterial milieu of colon



Normally, good bacteria like Bacteroides fragilis
- get killed and unnecessary coliform starts to grow



These coliforms result in excess D- lactate formation



D-lactate absorbed from colon



which can cause Neurological features

4) Hypergastrinemia:

- Normally, small intestinal hormones keep a check on Gastrin Secretion (inhibits)
- Acid from parietal cell can also keep a check on Gastric secretion (inhibits)
- In small intestinal resection, all these hormones which inhibit Gastrin are absent
- Acid is not being secreted from parietal cell
- So, Antrum produces lots of Gastrin → Hypergastrinemia

- Loss of duodenum → Fe absorption defective
- Loss of jejunum → Ca^{+2} / Folate / ADEK absorption defective
- Loss of Ileum → Loss of Bile Acid / vit-B₁₂

- Loss of Iliocecal valve



Results in bacteria migration from colon to small intestine



Results in SIBO (Small Intestinal Bacterial overgrowth)

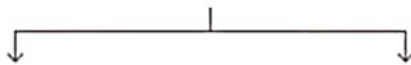
- Deficiency of vitamin-K is rare



Because Bacteria can Synthesize vitamin K

management:

Depends on colon



Colon present

- Complex carbohydrates
35 kcal/kg/day + fibre



Gets converted into
short chain fatty acids
in the colon and gets
absorbed

- Intact Protein
- medium chain Triglycerides

Colon Absent

- Intact Protein
- Long chain triglycerides
- But, most often
Total parental Nutrition
is given

- Drugs approved - GLP - 1 Analogue - Teduglutide



maximally slows the transit time



more time for absorption

- Also known as Stagnant bowel syndrome/ Blind loop Syndrome
- Jejunal Aspirate of $> 10^5$ CFU/ml
- most common organism - Enterobacteriaceae Pseudomonas
- In case of Enterobacteriaceae } Jejunal aspirate of $> 10^3$ CFU is
Pseudomonas } enough

Causes:

1) Altered anatomy:

- Short bowel syndrome
- Any surgery which results in ileocecal valve loss
- Blind loops
- Jejunocolic fistula
- Diverticula

2) Dysmotility:

- Diabetes mellitus
- Scleroderma
- Hypothyroidism

3) Hypochlorhydria:

- In case of long-term acid suppression

4) Immunodeficiency Conditions:

- HIV

5) Multifactorial:

- Coeliac disease
- Parkinsons disease
- Bacterial overgrowth in small intestine



These bacteria deconjugate the conjugated bile acids



So, no conjugated bile acids in small intestine



No micelle formation



Fat malabsorption



Patient presents with diarrhea and steatorrhea

- Bacteria utilises vitamin- B_{12}



Patient presents with macrocytic Anemia
Cobalamine deficiency

- These Bacteria also synthesize folate & vitamin K
 - ↑ Folate levels
 - ↑ vitamin K levels

Diagnosis:

1) Jejunal Aspirate:

- >10 CFU/ml $\Rightarrow$ Gold standard

2) Lactose hydrogen breath test:

Due to bacterial overgrowth in small intestine



Carbohydrate are metabolised in small intestine by these bacteria



Absorbed into blood



H_2 is seen in breath

3) urinary indican levels: High

- Due to Tryptophan metabolism by intestinal Bacteria

Treatment:

- Antibiotics for 7 -10 days
- Drug of choice: **Rifaximin**

Antibiotic Regimens for SIBO

Ciprofloxacin (250 mg twice daily)
Norfloxacin (800mg once daily)
metronidazole (250 mg 3 times daily)
Trimethoprim / Sulfamethoxazole (160/800 mg twice daily)
Doxycycline (100mg 2 times daily)
Amoxicillin-clavulanic acid (500 mg 3 times daily)
Tetracycline (250 mg 4 times daily)
Neomycin (500 mg 2 times daily)
Rifaximin (800 -1200 mg once daily)

- macrolides are not recommended

IRRITABLE BOWEL DISEASE

IBS

00:00:13

- Functional bowel disorder
- Overlapping symptoms
- F >> m
- First onset before 45yrs
- Abdominal pain is the key symptom for IBS
- It is a functional disorder, not a structural disorder
- It is generally associated with Fibromyalgia, Chronic fatigue syndrome, anxiety disorders & GERD
- For IBS to be diagnosed, the symptoms should be started before 45 years of age
- It is like the "manifestation of stress in G.I.T"

Rome IV criteria IBS:

- Recurrent "abdominal pain", on average of at least 1 day / week in the last 3 months associated with 2 or more of the following:
 - Related to defecation
 - Associated with a change in stool frequency
 - Associated with a change in stool form (appearance)

Criteria should be fulfilled for the last 3 months with symptom onset over 6 months prior to the diagnosis

Abdominal pain:

- mostly Episodic, crampy lower abdominal pain
- Exacerbated by eating / Emotional stress
- Relieved by defecation
- Change in the frequency / Form of stool
- Key clinical symptom in IBS: Abdominal pain
- Consistent clinical feature of IBS: Altered bowel habits

Altered bowel habits:

- most consistent feature of IBS
- Characterised by week or months of constipation with incomplete evacuation interrupted by brief periods of diarrhea
- It usually manifests like
 - Day time diarrhea
 - Small volume stools
 - mucus in large amount

Other related symptoms:

- Abdominal distension / Belching
- Dyspepsia / Heart burns
- Nausea / Vomiting

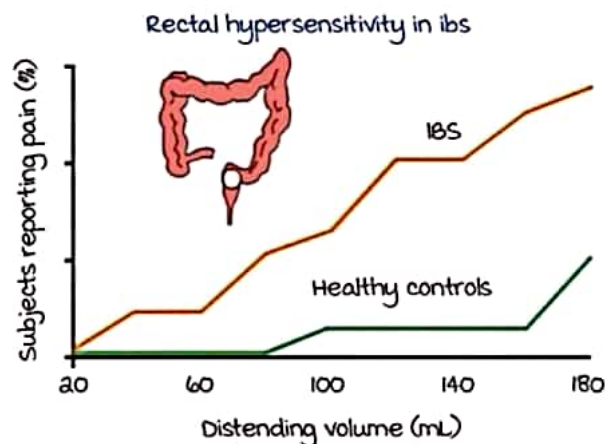
Never consider following symptoms as IBS:

1. Symptoms after 45yrs
2. Nocturnal Diarrhea
3. Large volume Diarrhea
4. Blood in stool
5. Steatorrhea / malabsorption
6. Anemia / wt. Loss in the patient
7. Patient with Fever / $\uparrow$ in ESR

Calprotectin (marker of inflammatory bowel disease) & serum crp levels will absolutely be normal in case of irritable bowel symptom

Pathophysiology of IBS:

00:19:08



- Exact pathophysiology of IBS remains uncertain
- **visceral hypersensitivity**: Enhanced pain sensitivity of the gut may play an important role in the development of chronic abdominal pain in IBS
- Graph: In normal pt's the stool distending volume of 100ml didn't cause much pain but in IBS pt's (orange) a distending volume of 100ml causes pain. It shows the Rectal Hypersensitivity
- Increase colonic motor potentials
- In brain, central activation of the **cingulate cortex**
- **Serotonin** containing **enterochromaffin cells** are increased
- **vanilloid channels (TRPV1)** are also implicated

Management of IBS

00:25:13

- mainstay of treatment remains **lifestyle & diet modification**

Fodmap diet of IBS:

- Fermentable oligosaccharides Disaccharides monosaccharides and Polyols
- FODMAP Diet should be **avoided** in IBS

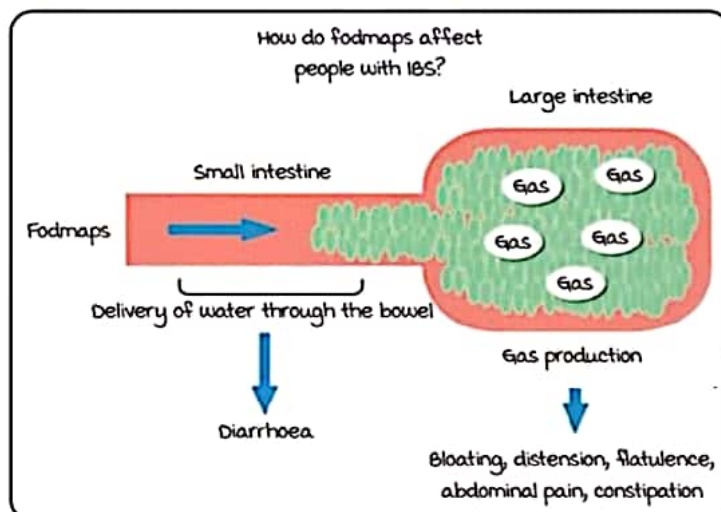
↑ in FODMAP



Not absorbed in small intestine



In colon, because of a lot of carbohydrates from FODMAP diet, the food gets fermented and produce gas



Examples of FODMAP foods:

1. Fruits with lots of free fructose – Apple, Honey, Cherry
2. Milk and milk products with lactose
3. Nuts, cereals, legumes, bananas, asparagus

Drugs in the treatment of IBS:

- Usage of drugs in the treatment of IBS mainly depends upon whether the IBS is diarrhea predominant or constipation predominant

IBS-C (constipation)

1. psyllium husk
2. peg laxatives
3. Tegaserod – $5HT_4$ agonist

Not in use because of cardiotoxicity

4. Lubiprostone – Bicyclic fatty acid which activates Cl^- channels $\rightarrow \uparrow$ influx of Na^+ & Cl^- into bowel

5. Linaclotide – Guanyl cyclase agonist
 $\downarrow$
 $\uparrow cGMP$

IBS-D (Diarrhoea)

1. Alosetron – $5HT_3$ antagonist
Not used now because it is associated with increased incidence of ischemic colitis
2. Loperamide – used at a dose of 2gms, 45 minutes before every meal
3. Eluxadoline – New drug, opioid μ receptor agonist

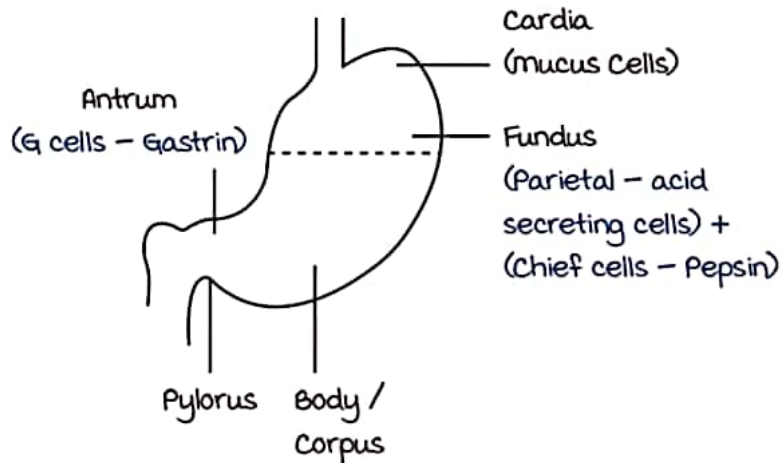
- Antibiotics have no role in IBS
- Antispasmodics like dicyclomine may be useful
- Prebiotics and probiotics have no role in IBS
- Antidepressants like TCAs have found to be useful in IBS

STOMACH

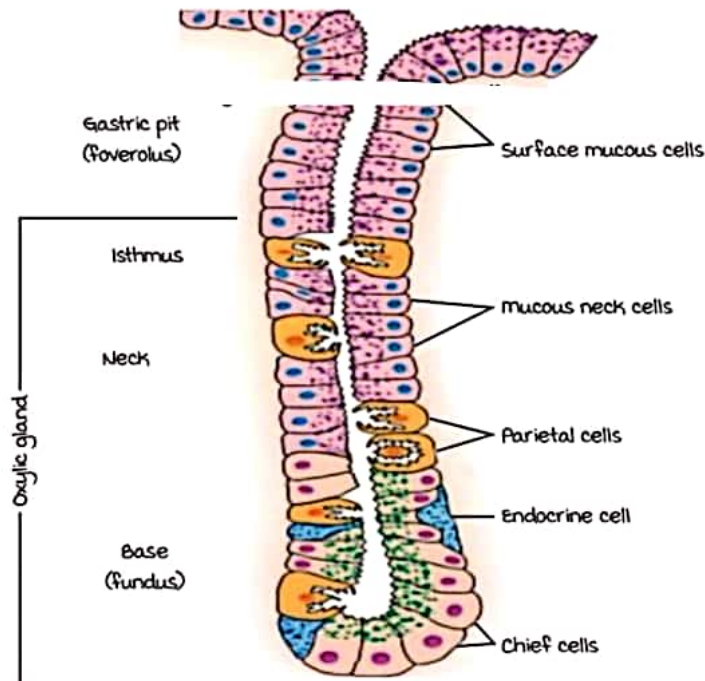
Stomach – Normal

00:00:52

- Cardia – mostly mucus & Endocrine glands
- Antrum – mostly G-cells – Produce Gastrin



- Body – All types of cells
 - Parietal cells / Oxyntic cells – Acid, Intrinsic Factor
 - Chief cells – Pepsinogen
 - ECL cells – Histamine
 - mucus cells
 - G-cells



- Gastric glands in the body of the stomach are known as **Oxyntic glands** because they have a lot of oxyntic cells
- In the oxyntic glands, Parietal cells are seen in the **Neck or, isthmus** chief cells at the **base of the gland** mucosal cells are seen at the **surface**
- 3 layer of gastroduodenal mucosal defence
 - Pre epithelial layer
 - Epithelial layer
 - Subepithelial layer

Gastritis and peptic ulcer disease

00:08:54

I. Acute gastritis:

It is an acute inflammation of the gastric mucosa

which is predominantly associated with upper GI symptoms and histologically there is infiltration by the neutrophils

- Very often, it is a **superficial** inflammation
- MC cause for acute gastritis - **NSAID's**
- 2nd MCC is - **Infection** - MC **H. pylori** - Very often its self limiting
- Serious cases are seen in Immunocompromised - **CMV1, HSV** are the agents

Acute phlegmonous gastritis:

- Acute, severe, progressive inflammation of gastric wall leading to stomach wall necrosis
- Associated with high mortality
- Seen in immunocompromised
- Caused by **Streptococcus**
- Characterised by abdominal pain, vomiting, high grade fever, sepsis and septic shock
- On CT : Thickening of gastric wall with low intensity areas and gas formation
- This is the **most fulminant form of gastritis**

Chronic gastritis:

- Superficial involvement of the gastric mucosa with lymphocytes & plasma cells
- Chronic gastritis can progress to atrophic gastritis, Intestinal metaplasia, dysplasia and gastric cancer
- There are 2 types of chronic gastritis - Type B is more common than type A

Chronic gastritis - type A :

- Less common than type B
- It is associated with Autoimmune disease - more often with pernicious anemia
- Very strong correlation with HLA-A - 8 and HLA DR - 3
- It is characterised by antibodies predominantly against Fundus / Body; Antibodies against Parietal cells; So, IF and acid are not produced
- IF - megaloblastic Anemia
- Acid - Achlorohydria
- Feedback inhibition of gastrin release from antral G-cells by acid gets affected, leading to hypergastrinemia
- Hypergastrinemia leads to carcinoid tumor

Type B gastritis:

- more common than type A
- It is associated with H. Pylori
- Starts as an antral predominant gastritis then it progresses to pangastritis
- This can lead to atrophic gastritis, Intestinal metaplasia and gastric adenocarcinoma
- MALToma is a consequence of non-atrophic pangastritis due to H. pylori
- Gastritis which presents with intestinal obstruction - Eosinophilic gastritis
- Gastritis due to involvement of plasma cells leading onto tumor like appearance with pseudotumor endoscopy appearance is - Russell body gastritis

- Commonest cause of Granulomatous gastritis – Crohn's disease
- Gastritis associated with celiac disease – Lymphocytic gastritis

Menetrier's disease

00:23:51

menetrier's Disease (aka
Hypertrophic Gastritis)



- Also known as Hypertrophic gastritis
- Shows large tortuous mucosal folds predominantly in the body & fundus sparing the antrum
- males >> Females with age of 40-60 years
- Predominantly mediated by TGF - α
- Histological finding: Foveolar Hyperplasia
- In children, this is due to CMV infection

Clinical features:

- Patient will have Hypersecretion of mucus leading to lots of protein loss
- This is protein losing gastropathy
- Upper GI Symptoms + Hypoalbuminemia + Edema in a middle aged man suggestive of Menetrier's disease
- It is a Pre - malignant condition

DIAGNOSIS :

- The IOC is Endoscopy with full thickness biopsy

DOC :

- The disease is caused by TGF α which acts through EGFR pathway
- So, the DOC is EGFR inhibitor – Cetuximab

H. PYLORI AND MALTOMA

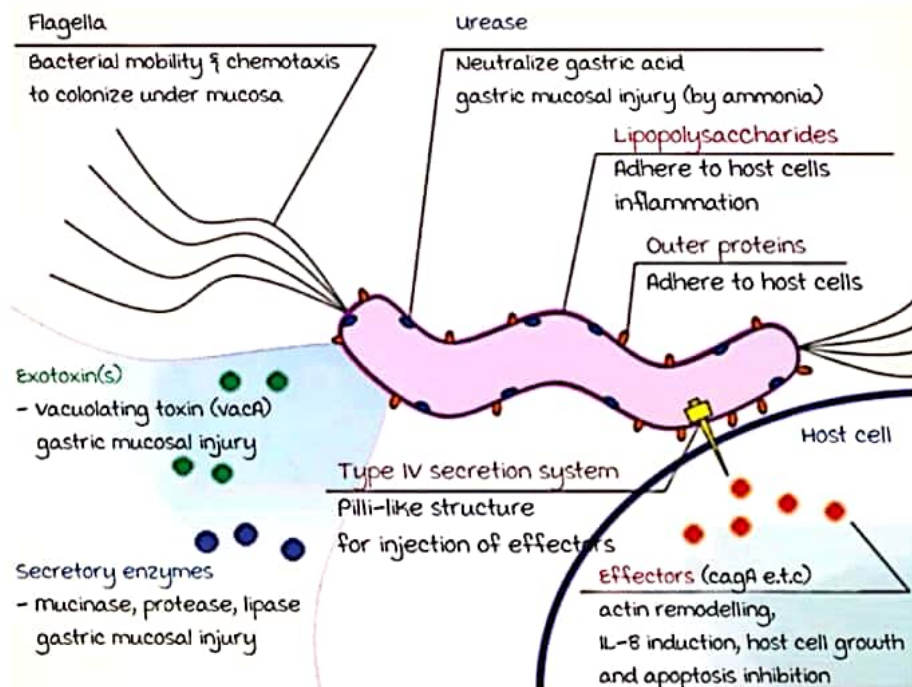
H. Pylori

"Gram negative"

microaerophilic

Rod shaped

[Catalase +ve; Oxidase +ve; Urease +ve]



Generally, resides in the antrum, migrate proximally inside the antrum → Deeper portions of the mucosal gel

urease neutralize gastric acid by ammonia to survive in stomach

In the Antrum migrate proximally using flagella →

flagella is responsible for mobility and chemotaxis etc

To adhere onto host cell – Two factors

1. LPS

2. OMP – Outer membrane Protein

Colonization of gastric mucosal epithelium → Chronic superficial gastritis

it is protective against.

1. GERD
2. Barret oesophagus
3. Adeno carcinoma of esophagus
4. Adeno carcinoma of cardia of stomach

Colonization Dependent on socio economic status

- Transmitted by feco-oral Route
- 80% of our population are actually having H. pylori

Toxins produced by H. Pylori

00:10:15

Vacuolating toxin (vacA)

- Gastric mucosal injury
- Secretory enzymes
- mucinase, Protease, Lipase
- Gastric mucosal Injury



2. Type IV secretion system

- Pilli-like structure
- For injections of effectors

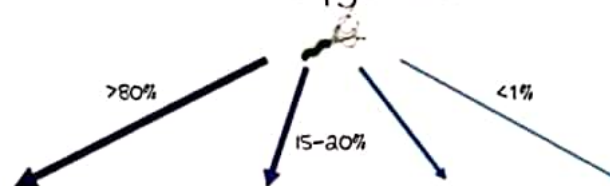
3. Effectors [cagA]

- Actin Remodelling
- IL-8 Induction
- Host cell Growth and Apoptosis Inhibition

Clinical outcomes of H. Pylori infections

00:12:04

The clinical outcomes of Helicobacter pylori Infections



Asymptomatic or chronic gastritis



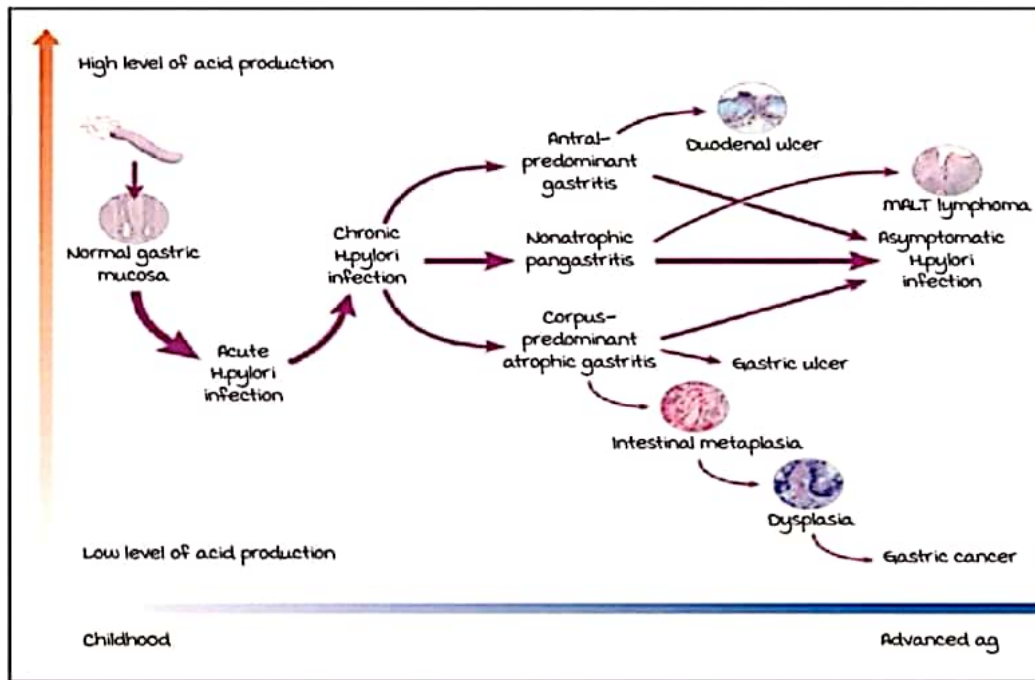
Chronic atrophic gastritis intestinal metaplasia



Gastric or Duodenal ulcer



Gastric cancer MALT lymphoma



H. pylori predisposing factors:

- Colonization induced chronic superficial gastritis [$>80\%$] but only $15-20\%$ develop peptic ulcer
- Ammonia production and alkalization is the first step
- 80% of population in developing countries Infected by 20 yrs
- Elevated cytokines in gastric epithelium of affected individuals [IL-1 and IL-8] has 11 Pre-disposition

Oneliners:

- $70-80\%$ of duodenal and $60-70\%$ of gastric ulcers are due to H. pylori
- Gastric adenocarcinomas are more common in body or fundus or corpus
- maltoma is a type of lymphoma associated
- Biopsy urease Test is the most convenient, simple and quickest Test
- Stool antigen test is the best for follow up
- Antral predominant gastritis leads to duodenal ulcer
- Corpus predominant gastritis leads to gastric ulcer; Adeno carcinoma
- Non atrophic pangastritis leads to maltoma

IOC: upper GI endoscopy + Biopsy urease Test

most specific and most sensitive Test

If Test result positive → The patient colonized by H.pylori

- Symptoms due to H. pylori → Eradicate
- If it is asymptomatic colonization, eradication is upto physicians discretion
- in young patient if symptoms are not due to H. pylori better not to treat
- If it is due to H. pylori then treat the patient

Role of histology:

- No much role
- "Warthin stain"

Role of culture:

- Even, after the repeated anti H.pylori regimes if the patient is still harbouring organism
- But, for practical purpose histology and culture are not required

TABLE

TESTS COMMONLY USED TO DETECT HELICOBACTER PYLORI

Test	Advantages	Disadvantages
Tests Based on Endoscopic Biopsy		
Biopsy urease test	Quick, simple	Some commercial tests not fully sensitive before 24h
Histology	may give additional histologic information	Sensitivity dependent on experience and use of special stains
Culture	Permits determination of antibiotic susceptibility	Sensitivity dependent on experience
Noninvasive Tests		
Serology	Inexpensive and convenient; not affected by recent antibiotics or proton pump inhibitors to the same extent as breath and stool tests	Cannot be used for early follow-up after treatment; some commercial kits inaccurate, and most less accurate than urea breath test
¹⁴ C II urea breath test	Inexpensive and simpler than endoscopy; useful for follow-up after treatment	Requires fasting; not as convenient as blood or stool tests
Stool antigen test	Inexpensive and convenient; useful for follow-up after treatment; may be useful in children	Stool-based tests are disliked by people from some cultures

Standard regime:

OCA Regime:

Omeprazole 20mg bd → [7-14 days]

Clarithromycin 500mg bd 14 days

Amoxicillin 1g bd

[or]

OCM Regime:

Omeprazole 20mg bd → 14 days

Clarithromycin 500mg bd

metronidazole 500mg bd

For clarithromycin resistance:

OBTM Regime:

Omeprazole; Bismuth subsalicylate; 14 days

Tetracycline; metronidazole

First line therapies

00:26:37

Regimen	Drugs	Dose	Days	FOA
Clarithromycin Triple	PPI [std/double dose] clarithromycin [500mg] Amoxicillin(1g) or metronidazole 500mg(TID)	BID	14	Yes
Bismuth [Quadruple]	PPI [std dose] Bismuth subcitrate [120-300mg] or subsalsalicylate [300mg] Tetracycline [500mg] metronidazole [200-500mg]	BID QID QID QID (250mg) TID to QID (500)	14 10-14	Yes No
Concomitant	PPI [std dose] Clarithromycin [500mg] Amoxicillin [1g] Nitroimidazole [500mg]	BID	10-14	NO

Sequential	PPI [std dose] PPI, clarithromycin (500mg) + Nitroimidazole 500mg	BID	5-7	NO
		BID	5-7	
Hybrid	PPI [std dose] PPI, Amox, Clarithro; Nitroimidazole	BID	7	NO
		BID	7	
Levofloxacin Triple	PPI std / double dose + Amox (1g) Levofloxacin (500mg) Amox (1g)	BID	5-7	NO
		BID		
Levofloxacin (sequential)	PPI std + double dose + Amox (1g) PPI, Amox, Levofloxacin (500mg) Nitroimidazole (500mg)	BID	5-7	NO

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Confirm eradication after 1 month of completion of treatment by following tests:

- urea breath Test [Radioisotope C_{13}]
Or
- Stool Antigen Test
Inexpensive
Convenient
Non invasive
Generally preferred test

Positive stool antigen test after one month implies drug resistance
Start second line treatment

If second line Regime not working → Go for culture and sensitivity

TABLE
Tests for Detection of *Helicobacter pylori*

Test	Sensitivity/ specificity, %	Comments
Invasive (Endoscopy/Biopsy Required)		
Rapid urease	80-95/95-100	Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds
Histology	80-90/795	Requires pathology processing and staining; provides histologic information
Culture	-/-	Time - consuming, expensive, dependent on experience; allows determination of antibiotic
Noninvasive		
Serology	>80/>90	Inexpensive, convenient; not useful for early follow-up
urea breath test	>90/>90	Simple, rapid; useful for early follow-up; false negatives with recent therapy (see rapid urea low-dose radiation with ¹⁴ C test)
Stool antigen	>90/>90	Inexpensive, convenient

Serology → Has no role

Because, patient will continue to remain
Positive even after eradication

Oneliners:

- most commonly used PPI Omeprazole 20mg Bd
- Dexlansoprazole is the recent PPI approved, most potent and delayed release, useful in GERD.
- Negative effect on antiplatelet effect clopidogrel
- Tenatoprazole is a irreversible PPI
- PPI long term use → Bone fracture; Hip fracture
- Short term use → Acute tubulo interstitial nephritis
- Electrolyte Imbalance → Hypomagnesemia

Drug Interaction:

Between PPI and clopidogrel

Clopidogrel activation requires CYP_{3A4}, which is affected by PPI.
So, should be careful while using PPI with clopidogrel

PEPTIC ULCER

Ulcer:

Ulcers are defined as breaks in the mucosal surface > 5 mm in size, extending into the submucosa.

Duodenal ulcers

1st portion of duodenum (95%) with ~ 90% located within 3 cm of pylorus

usually < 1cm (3-6 cm; giant ulcer)

Gastric ulcers

Distal to junction between antrum and acid secretory mucosa

Prepyloric area

Features	Gastric ulcer	Duodenal ulcer
Incidence	Less common	More common
Location	Antrum; lesser curvature	Anterior wall; 1 st part
Age group	middle age	middle or old age
male: Female	1:1	4:1
Association H. pylori	65%	85%-100%
malignancy	Common	Rare
Level of gastric acid secretion	mostly Normal	mostly increased

Cushing ulcer → Stress related

Curling ulcer → Burns

Kissing ulcer → Both anterior and posterior wall of duodenum

Perforation → Gastric ulcer > Anterior duodenal ulcer

Bleeding → Duodenal ulcer → Gastroduodenal artery (posterior)

Gastric ulcer → Left gastro epiploic artery

Dumping Syndrome:

Early (10–30min)

- Intravascular depletion

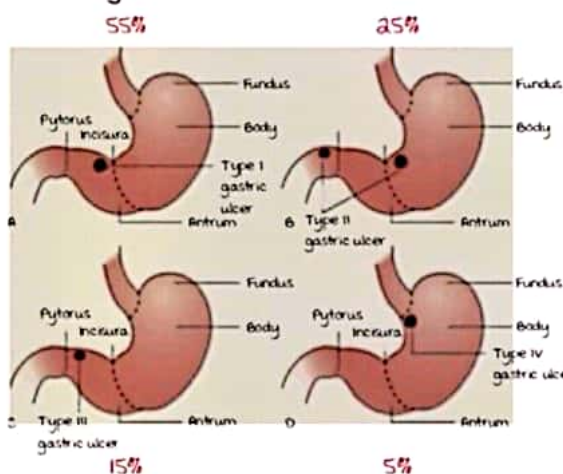
Late (2–3 hrs)

- Reactive hypoglycemia

Types of gastric ulcer (Daintree johnson)

00:06:24

Daintree johnson



- Type I
In the antrum, near lesser curvature, normal acid level
- Type II
Combine gastric and duodenal ulcer
High acid level
- Type III
Prepyloric
High acid level
- Type IV
Ulcer in the proximal stomach and cardia
normal acid level

- Type I most common

It is fundamental that any gastric ulcer should be regarded as being **malignant no matter how classically it resembles a benign gastric ulcer**

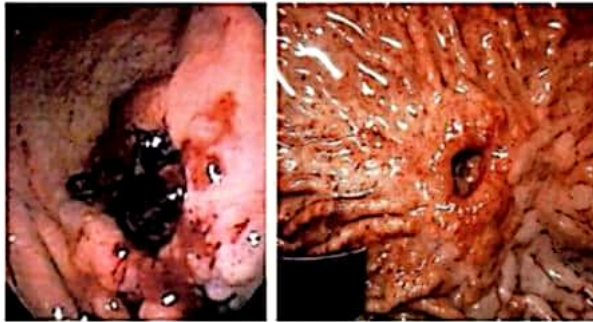
multiple biopsies should be taken, as many as 10 well targeted biopsies

Malignant gastric ulcer

00:08:11

mucosal folds	Effacing mucosal folds
margin	Irregular margin
Floor	Necrotic slough in the floor
Edges	Everted edges
Surrounding area	Shows nodules; ulcers and Irregularities
Size and extent	Large and deep

Gastric ulcers



COX - 1 Housekeeping (mucosal protection)

COX - 2 Inducible inflammation and mitogenesis under COX - 2

2 major Factor in duodenal ulcer

H. pyloric

NSAID

malignancy risk more is gastric ulcer

Gastric ulcers have normal or decreased acid output

Zollinger ellison syndrome

00:10:40

Gastrinoma (Gastrin secreting tumour)

80% sporadic

20% associated MEN - 1 syndrome

30-50 years affected

Female > male

60% malignant

Neuroendocrine tumour

Express chromogranin; Synaptophysin

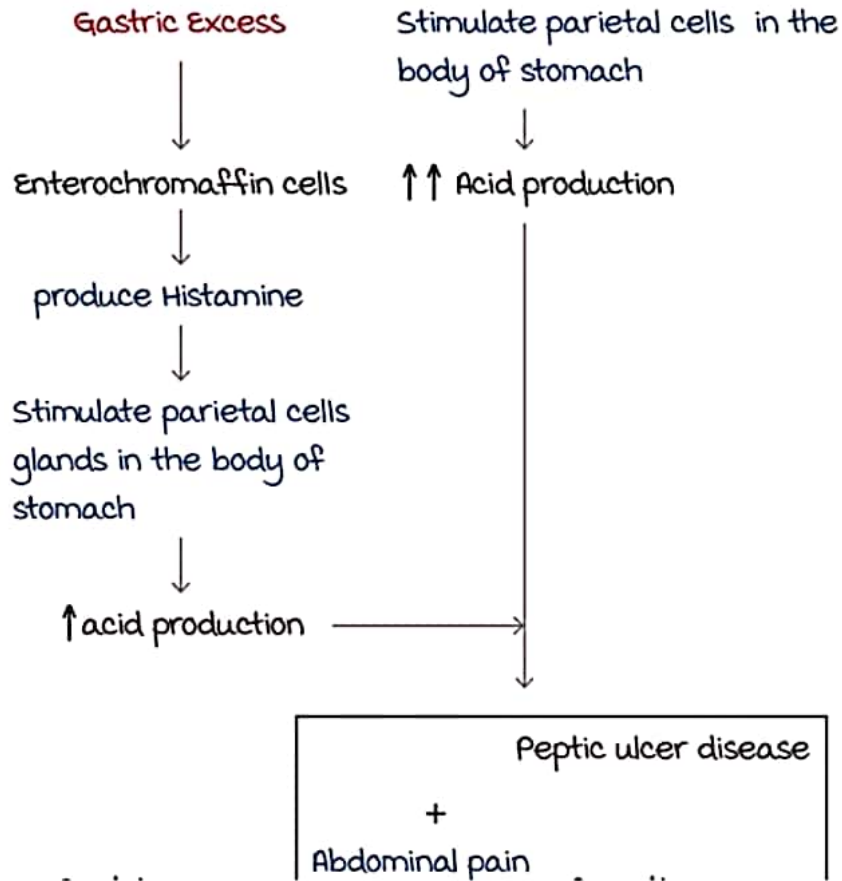
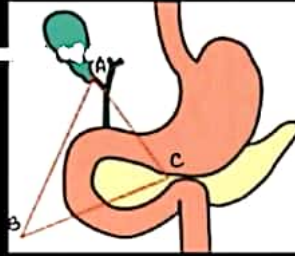
m/c location duodenum 1st part

20% coming from pancreas

m/c in Gastrinoma triangle / **Passaros triangle**

Gastrinoma triangle

- A - Junction of cystic duct and CBD
- B - junction of second and third portion of duodenum
- C - Junction of body and neck of pancreas



Duodenal gastrinomas: (70 - 80%)

Tends to be small; multiple; benign, MEN1 associated

Pancreatic gastrinoma: (60%)

Large; Solitary and malignant

Other points in ZES:

marker: Neuron specific enolase

80% in gastrinoma triangle

Duodenal lesions are smaller & less aggressive

Peptic ulceration is the m/c manifestation

Gastric carcinoids are m/c in MEN

Symptom abdominal pain → Peptic ulcer

Gastric hypertension → Gastric carcinoids, MEN 1
syndrome Associated

Peptic ulcer

unusual locations (D₂ and beyond)

Refractory to medical therapy

Recurrence

Diarrhoea (osmotic + secretory)

Small; multiple; duodenal; less aggressive/MEN - 1

Gastrin Radioimmunoassay:

Of acids suppressing medicines for 48 hrs

< 200 pg/ml Normal

200-1000 pg/ml Confirmatory Test (70%)

> 1000 pg/ml Gastrinoma (30%)

Screening Test of choice: Serum Gastrin level

Prior to screening test, patient should be off acid suppressing
medicines for 1 week

200-1000 pg/ml - Secretin stimulation Test (confirmatory Test)

Secretin stimulation test

00:21:53

Confirmatory Test

Secretin inhibits gastrin

Secretin stimulates or ↑ gastrin level in gastrinoma IV

Secretin over 30mins of gastrin levels ↑ by

> 200pg/ml is confirmatory

Localization of the tumour

00:23:27

Somatostatin receptor scintigraphy

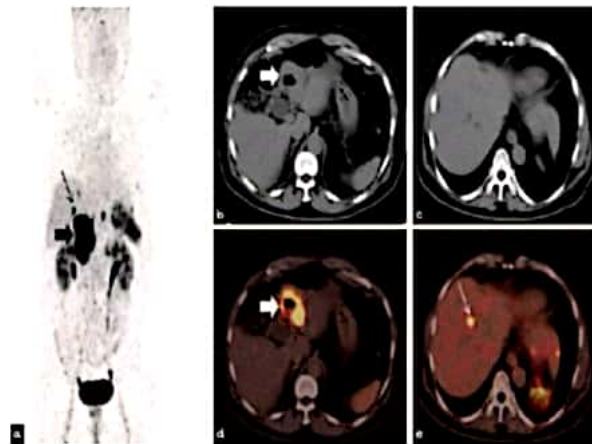
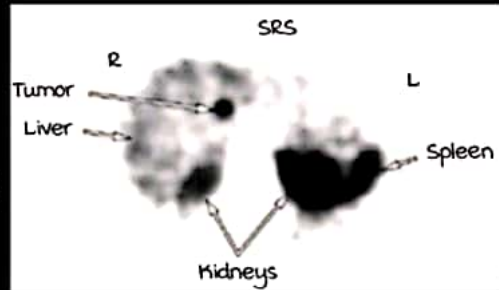
or

Ocreotide scan

IOC → Gallium - Dotatate PET/CT Scan

Somatostatin receptor scintigraphy "Ocreotide scan"

- Gastrinomas have somatostatin receptors
- Radioactively labeled ocreotide
- Single most sensitive study
- misses small duodenal gastrinomas



MEN syndrome associated duodenal gastrinoma are best localized by **Endoscopic ultrasound**

Few points:

- Basal acid output / maximal acid output : **No significance**
- Endoscopic ultrasound in MEN syndrome

Gastrinoma Treatment:

High dose PPI (Omeprazole 60 mg - 80 mg)
+/-
Octreotide

Definitive treatment: Surgery

Whipple surgery has the best outcome

In MEN - 1 → No role for surgery unless tumour > 2.5 cm

∴ High dose PPI followed by surgery
m/c site for metastasis - Liver

EMBRYOLOGY AND ANATOMY OF LIVER

Development of liver

00:02:03

Ventral wall of foregut
 ↓ at 3-4 weeks
 Proliferating endodermal bud
 called **hepatic diverticulum**

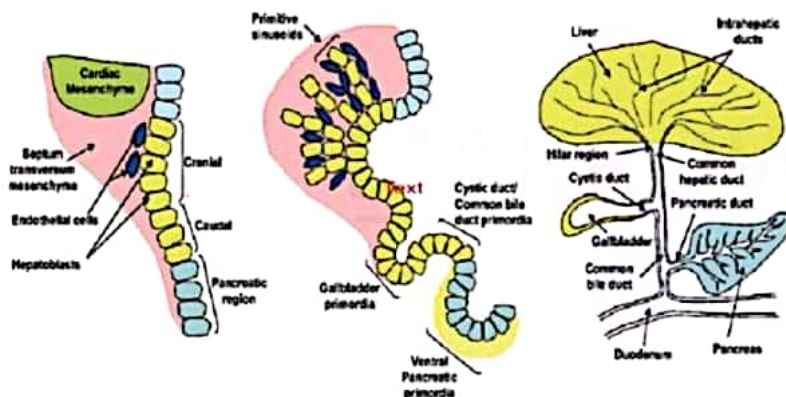
Cranial

- Liver
- Biliary tract

Caudal

- Gall bladder
- cystic duct
- Ventral pancreas

- Signal for development of hepatic bud comes from **cardiac mesenchyme**
 - **FGF** : Fibroblasts growth factor
 - **BMP - 7** : Bone morphogenic protein



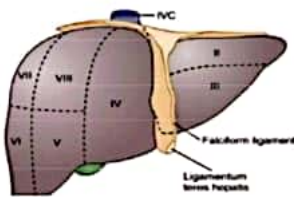
- Cords of **hepatoblasts** invade **septum transversum**
 (endoderm) (mesoderm)
- | | | |
|---------------------------|--|--|
| <p>hepatocytes</p> | <p>cholangiocytes</p> <ul style="list-style-type: none"> • TGF - β • NOTCH - 2 | <p>Connective tissue of liver</p> <p>stellate cells</p> |
|---------------------------|--|--|

- **Alagille syndrome** : Autosomal dominant
 < 6 months of age
 NOTCH - 2 pathway defect
 paucity of intrahepatic bile duct
 mental retardation / pulmonary valvular
 hypoplasia / visual field defects / growth defects

Anatomy of liver

00:15:37

- Lobes of liver :

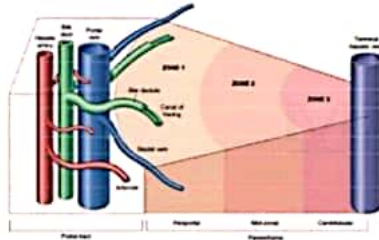


- Anatomical lobes

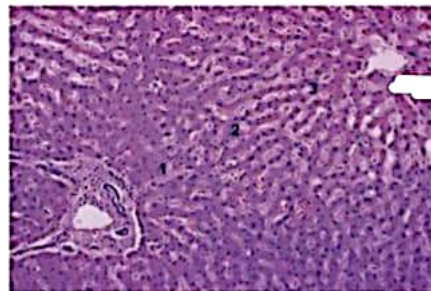
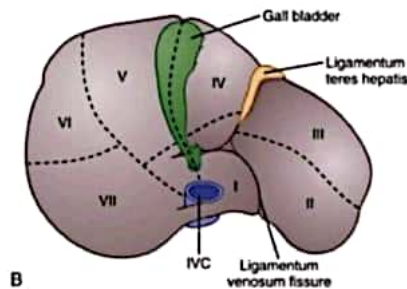
- falciform ligament
- Left : II, III
- Right : IV, V, VI, VII, VIII

- surgical lobes

- Cantlie's line from gall bladder to inferior vena cava (IVC)
- Left : II, III, IV, I
- Right : V, VI, VII, I



- I → caudate lobe → directly drains to IVC
- IV → quadrate lobe
- Basic structural and functional unit : Lobule



- Periportal hepatocytes - Zone 1
- midzonal hepatocytes - Zone 2
- Centrilobular (zone 3) zone is most vulnerable to hypoxia
- 70/40 ; 30/60 rule
 - 70% blood supply & 40% O₂ supply → portal vein
 - 30% blood supply & 60% O₂ supply → Hepatic artery
- Hepatic artery : anterior to portal vein, left to bile duct
- Glisson's capsule covers all structures except hepatic vein
- Cirrhosis → lobules are replaced by nodules

↓
Connected by fibrous septa

Cellular anatomy of liver -

- Three membranes

1. Contiguous membrane : tight junctions and gap junctions
2. Canalicular membrane : bile flow
3. Sinusoidal membrane (basolateral membrane)

- Space of disse : between sinusoidal membrane and sinusoidal endothelial lining
Stellate cells

- Stellate cells :

- situated in space of disse
- also called Ito cell

Vitamin A storing cell

Lipocyte

- In cirrhosis , activated stellate cells



produce TGF- β



Fibrosis (key event in cirrhosis)

- NK cells in liver : pit cells

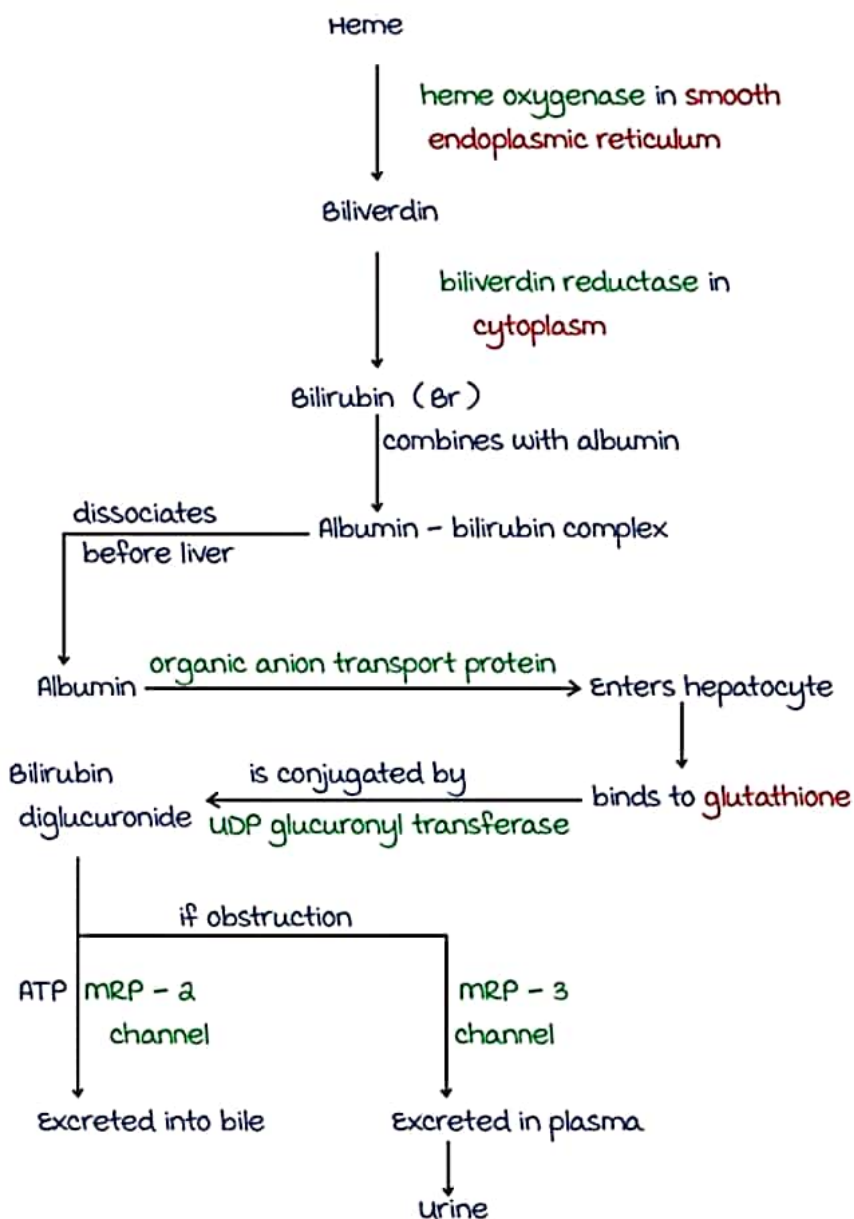
expresses CD56

LIVER PHYSIOLOGY

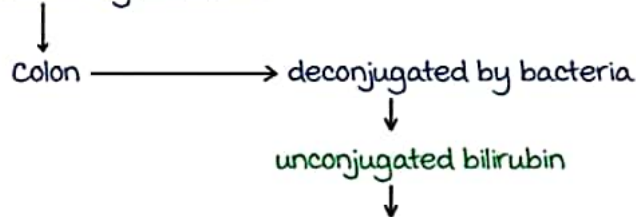
Bilirubin pathway

00:00:22

- Bilirubin → Heme degradation
80 % Hb
20 % heme containing proteins
- Bilirubin → 300 mg per day
4 mg / kg per day



- Bilirubin diglucuronide



Urobilinogen

- 80 % excreted in stool
- 20 % enters enterohepatic circulation
- Small amounts absorbed
- traces present in urine normally

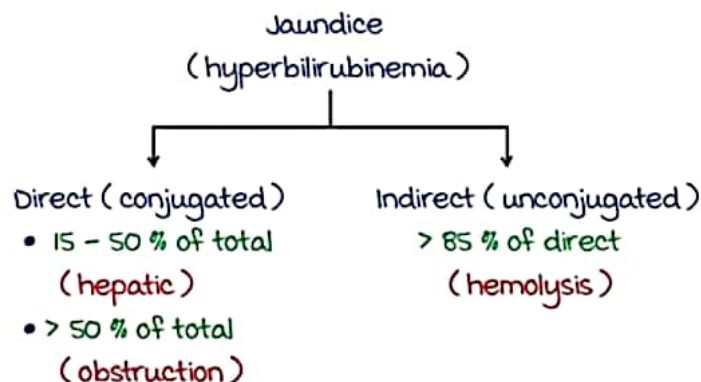
- Increased urobilinogen in urine → Hemolysis
Cirrrosis

Absent urobilinogen in urine → obstruction of biliary tree

Hyperbilirubinemia

00:09:10

- Bilirubin estimation
 - Classically, Van den Bergh / Diazo reaction
 - more recently, HPLC (High performance liquid chromatography)
- Normal values
 - Total Bilirubin = 1 - 1.3 mg / dL
 - Indirect bilirubin = 0.2 - 0.9 mg / dL
 - Direct bilirubin = 0 - 0.3 mg / dL



- most proteins produced by liver are positive acute phase reactants.
 - Exception of 4 proteins that are negative acute phase reactants.
 They are :
 - 1) Albumin
 - 2) Transferrin

- 3) A F P (alpha fetoprotein)
- 4) Transthyretin

- **Delta bilirubin**: variant of direct bilirubin with long half life
 - $t_{1/2}$ of normal bilirubin = 4 hours
 - $t_{1/2}$ of delta bilirubin = 14 - 21 days
- In certain patients it may take longer time for bilirubin to return to normal following clinical recovery.
- High total serum bilirubin levels correlates with poor outcome.

LIVER FUNCTION TEST

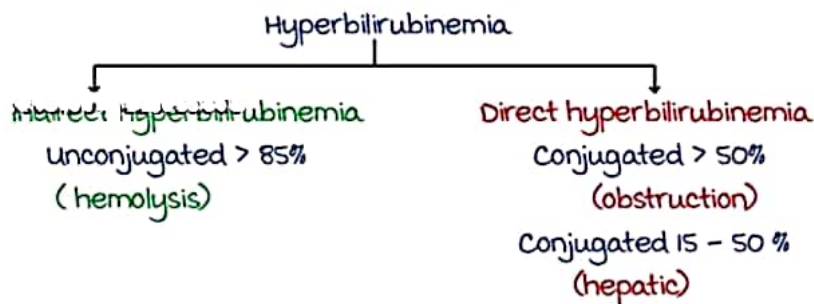
Serum Bilirubin

00:00:59

- method of estimations :
 - **van den Bergh** reaction (Diazo reaction)
Van den Bergh reagent + Blood $\longrightarrow$ Purple
(direct / conjugated)
Van den Bergh + alcohol + Blood $\longrightarrow$ Total bilirubin

Total - direct $\longrightarrow$ Indirect bilirubin .
 - **High performance liquid chromatography** (gold standard)
- Normal value :
 - Total bilirubin $\longrightarrow$ 1 - 1.3 mg/dl
 - Direct bilirubin $\longrightarrow$ 0 - 0.3 mg/dl
 - Indirect bilirubin $\longrightarrow$ 0.2 - 0.9 mg/dl
- Variant - **delta bilirubin** $\longrightarrow$ $t_{1/2} = 14 - 21$ days
may take extra time for bilirubin to come back to normal after recovery
- $t_{1/2}$ (half life) of normal bilirubin = 4 hours

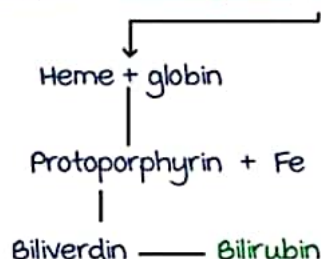
Hyperbilirubinemia :



Indirect hyperbilirubinemia

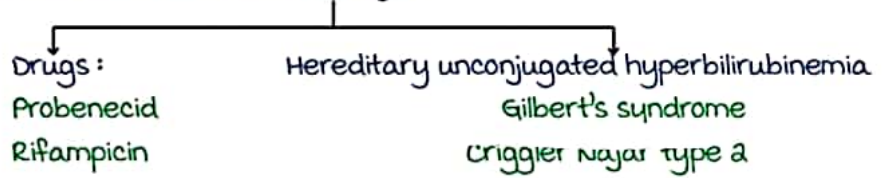
00:08:08

- Indirect bilirubin > 85% total
- When associated with **extravascular hemolysis**



- LDH +++
- haptoglobin ↓↓ → Specific for hemolysis
- Coomb's test → autoimmune hemolysis

- When not associated with hemolysis



- High serum total bilirubin level correlates with poor outcome

Liver Enzymes

00:13:31

Aminotransferases :

ALT :	AST
Alanine amino transferase SGPT	Aspartate amino transferase SGOT
Cytoplasm	Cytoplasm and mitochondria Liver
Liver specific	Skeletal muscle : rhabdomyolysis Cardiac muscle : MI

- In a healthy person :

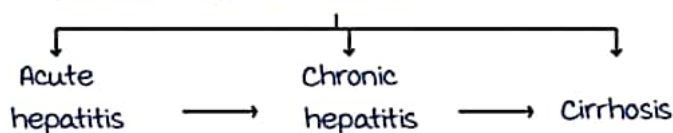
- ALT
- AST
- ALT > AST

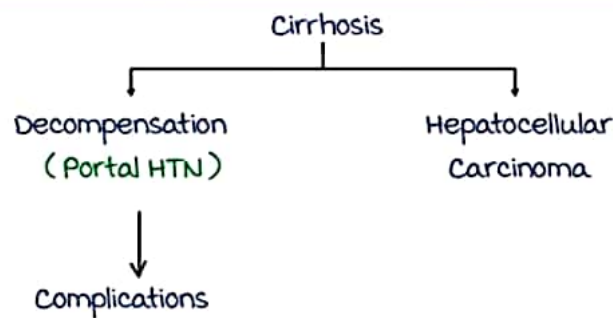
AST is more rapidly cleared by the reticuloendothelial system.

Acute hepatocellular injury

00:18:57

- Course of most liver disease





- In acute hepatitis :
 - ALT and AST $\longrightarrow$ very high $\longrightarrow$ > 1000 IU/L
 - When ALT and AST $\longrightarrow$ moderately high $\longrightarrow$ bad prognosis
less viable hepatocytes
- Causes :
 - 1) Acute hepatocellular injury
 - Virus
 - drugs
 - toxins
 - ischaemia
 - 2) Acute bile duct obstructions .
- usually , $ALT > AST$.
When underlying chronic alcoholic liver disease $\longrightarrow$ $AST > ALT$
- In alcoholic liver disease :
 - AST and ALT levels $< 300 - 400$ IU/L
 - When $AST / ALT = 2 : 1 \longrightarrow$ in acute hepatitis is mostly suggestive of alcoholic hepatitis
 - When $AST / ALT = 3 : 1 \longrightarrow$ diagnostic of alcoholic hepatitis
 - $AST > ALT$ in alcoholics because of pyridoxal phosphate deficiency .
 - Acute injury on chronic liver - ALT & AST > 1000 , $AST > ALT$

Chronic Hepatitis

00:31:29

- Clinically present with fatigue ; usually asymptomatic
- ALT and AST are elevated up to 5 times normal < 150 IU/L
- Causes :
 1. NASH : Non-alcoholic steatohepatitis
 2. Chronic viral hepatitis (B or C)
 3. Wilson's disease
 4. Autoimmune hepatitis
 5. Hemochromatosis

- When $AST > ALT$ in chronic hepatitis $\longrightarrow$ **Cirrhosis**
because of impaired hepatic blood flow and decreased sinusoidal uptake of AST
- High ALT and AST but < 150 in the absence of chronic hepatitis :
 - Celiac disease
 - Hyperthyroidism
- Isolated high AST $\longrightarrow$ **rhabdomyolysis, MI**

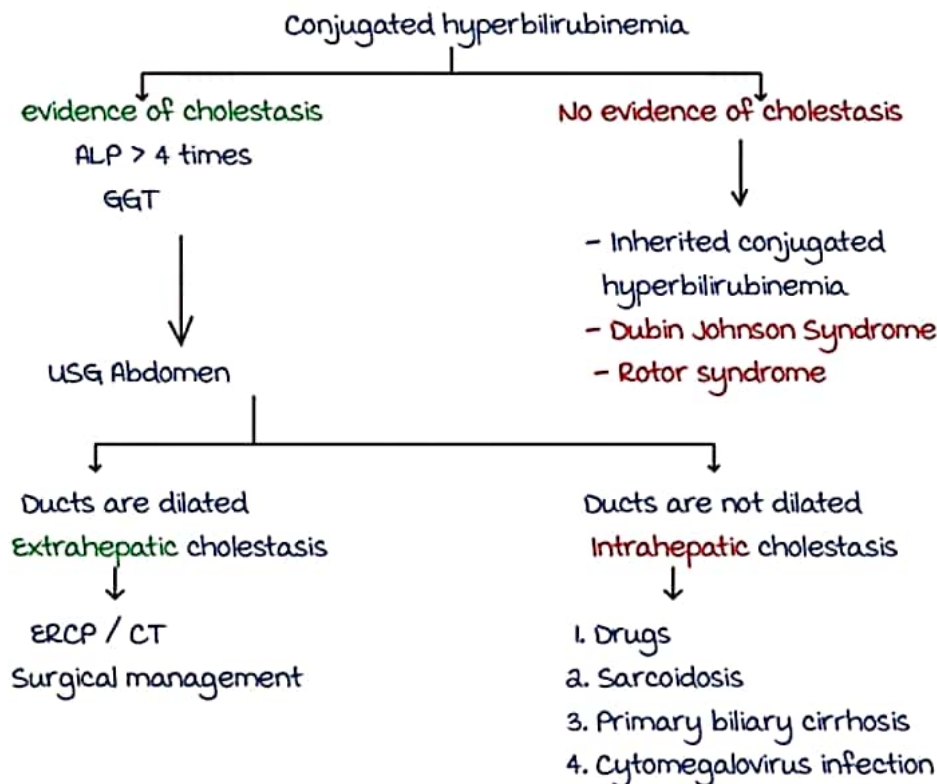
Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Alkaline Phosphatase (ALP)

00:41:37

- Normal value $\longrightarrow$ **40 - 140 IU/L**
- Physiological increase in
 - less than 4 times upper limit of normal
 - can be seen in pregnancy
blood group O
elderly ($> 70y$)
adolescent age
after heavy meal
- Sources of ALP
 - 1) Liver (canalicular membrane)
 - 2) Bone
 - 3) Intestine
 - 4) Kidney
 - 5) Placenta
- High ALP $\longrightarrow$ Possible $\longrightarrow$ Confirmation with :
 - > 4 Times normal **Cholestasis** 1) **GGT** : Gamma glutamyl transferase
Specific for cholestasis
 - 2) 5' nucleotidase also produced by liver & bone
- Reduced ALP $\longrightarrow$ Acute hepatitis in **Wilson's disease**

- Direct bilirubin = >50% of total



Drugs causing cholestasis

- 1) Simple gland Cholestasis
 - Anabolic steroids
 - Estrogen
- 2) Cholestatic hepatitis
 - Azathioprine
 - NSAIDs - Piroxicam
- 3) Granulomatous hepatitis
 - Allopurinol
 - Phenytoin
 - Procainamide
 - Sulfonamides
- 4) Vanishing bile duct syndrome
 - Erythromycin
 - Amoxicillin / Clavulanate

S. albumin, Total proteins and globulin

- Serum albumin :
 - 15g / day
 - molecular weight = 69,000
 - low albumin is a marker of chronicity
 - is a negative acute phase reactant
- globulins :
 - Polyclonal hypergammaglobulinemia → Autoimmune hepatitis
 - monoclonal hypergammaglobulinemia → Blood dyscrasias

a. PTT, PT, INR, Platelet count

- Thrombocytopenia → One of the first markers of portal hypertension

	Acute hepatitis (E)	DIC
PT / aptt / INR	↑	↑
S. fibrinogen	normal	↓ ↓
S. Fibrin degradation products	normal	↑ ↑
D - dimer	normal	↑ ↑
Factor VIII	normal	↓

- In vit K deficiency → PT is elevated
aPTT is normal
- MELD Score : acute hepatitis prognosis
Parameters - INR
S. bilirubin
Creatinine

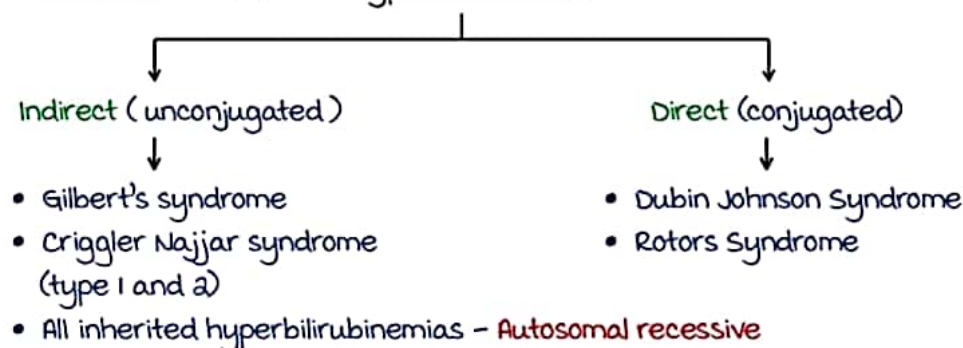
Fibroscan And Other Tests

01:04:03

- Also called **transient elastography** to look for cirrhosis
- Fibrospect 2 : blood markers of cirrhosis
 - 1) Hyaluronan
 - 2) α_a - microglobulin
 - 3) Tissue inhibitor of metalloproteinase - 1
- Quantitative liver function tests :
 - Indocyanine green clearance
 - galactose elimination capacity
 - Caffeine clearance
 - Lidocaine metabolite formation
 - Aminopyrine breath tests
- **Bile acids** - quantitatively to assess hepatic reserve
increased in cholestasis

INHERITED HYPERBILIRUBINEMIA

Classification of inherited hyperbilirubinemia



Gilbert's syndrome

00:01:22

- Due to **deficiency of UDP glucuronyl transferase** (10-30% of normal)
- **mild** unconjugated hyperbilirubinemia

↓
< 3 mg/dL - 85% or above is indirect bilirubin

- Fasting and infection - **deepens** jaundice
- Benign condition
- Liver function test (LFT) - **Normal**
- Hepatic histology - **Normal**, **Lipofuscin** in hepatocyte
- Good prognosis
- **Phenobarbitone** (enzyme inducer) can be used for treatment

Crigler najjar syndrome type 1 and 2

00:07:47

Crigler Najjar Syndrome type 1

- **Complete deficiency of UDP glucuronyl transferase** (Therefore phenobarbitone has no role)
- Serum bilirubin > 20 mg/dl
- Death within 1-2 yrs
- C/F- Kernicterus
- Treatment - **Liver transplantation**
- **Least common type**
- patients planned for liver transplant-phototherapy, tin protoporphyrin (Hemeoxygenase inhibitor)

Crigler Najjar Syndrome type 2

- **AR**
- < 10% of normal UDP glucuronyl transferase
- Serum bilirubin : 7 - 10 mg/dl (does not exceed 20 mg/dl)

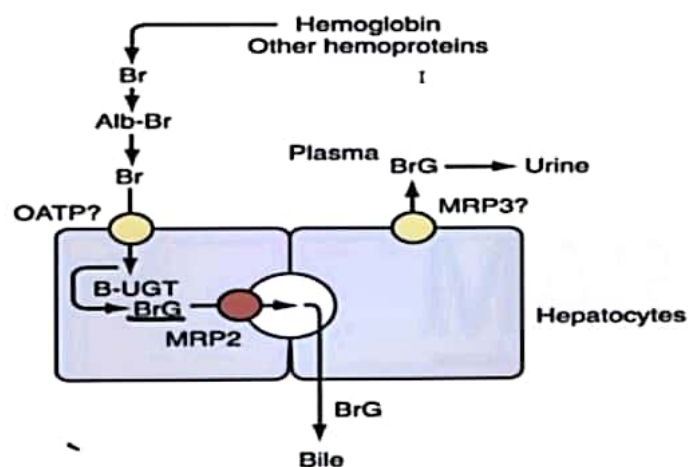
- C/F - Jaundice (can present as late as 30 yrs)
- LFT - Normal
- Histology - Normal
- Good prognosis
- Good response to phenobarbitone
- Pigmented bile in duodenum
- No kernicterus

Dubin Johnson syndrome

00:15:22

- AR
- mutation in **ABCC₈ gene / MRP₂ protein** - defective
(Present on canalicular membrane)

↓
Cannot excrete conjugated bilirubin into bile
↓
Conjugated hyperbilirubinaemia



- Conjugated hyperbilirubinemia - 4-7 mg/dl
- LFT - Normal
- Good prognosis
- Coarse pigment inside centrilobular hepatocyte

↓
due to **epinephrine**

↓
gives **dark pigmentation** to liver on gross examination

- **Bromsulphathetin test (BSP) positive**

↓
i) Normally : at - 45 mins - ↑
120 mins - ↓

ii) In Dubin Johnson Syndrome - levels are $\uparrow$ in 120 min $>$ 45 min

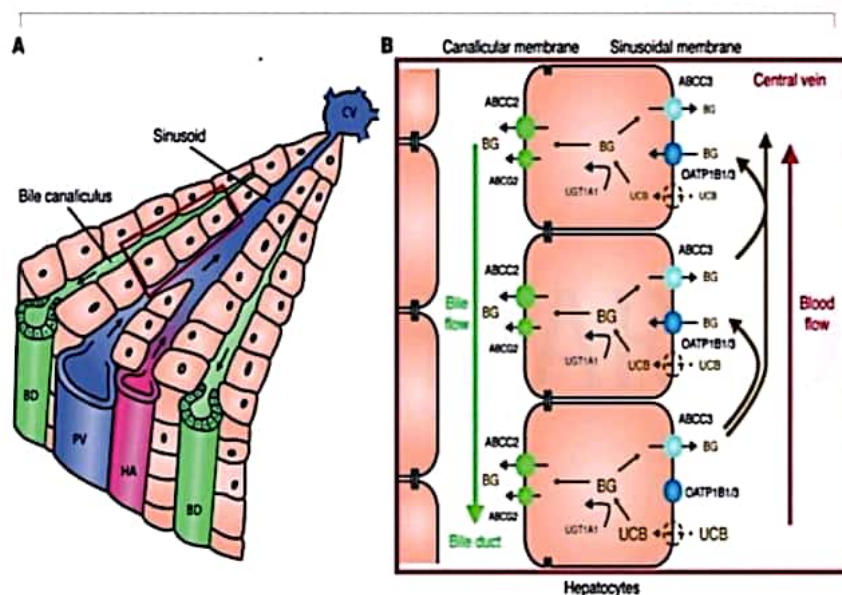
iii) Urine coproporphyrin excretion - type I $\gg$ III (Normally type III $>$ I)

- Oral Cholecystography - non visualisation of gall bladder and biliary tree.

Rotors Syndrome

00:23:42

- AR
- Conjugated hyperbilirubinemia - 4-7 mg/dl
- Defect in OATP (Organic Anion Transport Protein)



- OATP is required for subsequent uptake of conjugate bilirubin
- Liver biopsy and gross examination - normal
- BSP test negative
- Oral Cholecystography - normal
- Urinary coproporphyrin - I $\gg$ III (Total high)
- T_c HIDA Scan - No visualization of liver/ Gall bladder

ACUTE VIRAL HEPATITIS

- Acute hepatitis $\Rightarrow$ Hepatitis A and Hepatitis E

Hepatitis A Virus

00:01:51

- $\rightarrow$ Single stranded RNA virus .
- $\rightarrow$ Picornaviridae .
- $\rightarrow$ Non enveloped , heat sensitive virus . ($> 85^{\circ}\text{C}$)
- $\rightarrow$ mode of transmission : feco-oral
- $\rightarrow$ very rarely sexual / parenteral
- $\rightarrow$ vertical transmission $\rightarrow$ Never
- $\rightarrow$ Incubation period $\rightarrow$ 30 days.
 - 30 days $\rightarrow$ A
 - 40 days $\rightarrow$ E
 - 50 days $\rightarrow$ C
 - 60 days $\rightarrow$ B

Acute hepatitis :

- $\rightarrow$ most common cause worldwide $\rightarrow$ Hepatitis E (adults)
Hepatitis A (children)

Hepatitis A :

00:05:00

- $\rightarrow$ Prodromal stage $\rightarrow$ 2-3 days .
 - fever , myalgia , vomiting
 - followed by jaundice .
- LFT : 1. Bilirubin high
- 2. Hepatic Jaundice (15 - 50% conjugated)
- 3. Aspartate aminotransferase (AST) & Alanine aminotransferase (ALT)
more than 1000 ALT has to be more than AST .

clinically :- $\rightarrow$ Jaundice

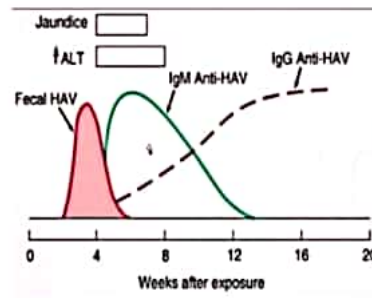
- $\rightarrow$ mild Hepatomegaly in 85% .
- $\rightarrow$ Extra hepatic manifestations (rarely)
 - rash or arthralgia .
- $\rightarrow$ Right upper quadrant tenderness .

Causes :-

- $\rightarrow$ most common cause of viral hepatitis in children
 - $\rightarrow$ Hepatitis A
- $\rightarrow$ most common cause of acute relapsing viral hepatitis .
 - $\rightarrow$ Hepatitis A
- $\rightarrow$ Incubation period of 4 weeks .

Differential diagnosis :

- virus → Hepatitis A ,
Hepatitis E , Hepatitis B
- Drug / toxin
- Ischaemia
- Autoimmune
- Wilson's disease
- Alcohol.



Investigation : - anti HAV IgM . → disappears in 12 weeks .

→ clinically → 8 weeks

- anti HAV IgG → recovered .

Note: Acute relapsing hepatitis

→ 2 in 1,00,000 → fulminant hepatic failure



Encephalopathy ± coagulopathy
within 7 days of onset of symptoms

→ very rarely → asymptomatic .

→ vaccine .

• Fulminant hepatic failure → 100 % mortality without transplant .

• model for end-stage liver disease (MELD) Score → INR , serum
bilirubin , creatinine
→ prognostic

• Vaccine :- HAVRIX vaccine → 1 ml , I.m .

2 doses → 0 , 6- 12 months

Pre exposure → more than 2 weeks prior to travel

Post exposure → within 2 weeks of exposure

Hepatitis Virus

00:17:20

- Hepeviridae under calcivirus
- Single stranded RNA virus
- Non enveloped .
- Destroyed by boiling (more than 85°C)
- 4 genotypes
- mode of transmission : Feco-oral
- rarely vertical
- No sexual or parenteral transmission
- Immune mediated injury to hepatocytes
- Incubation period → 40 days .
- Clinical picture is almost same as hepatitis A

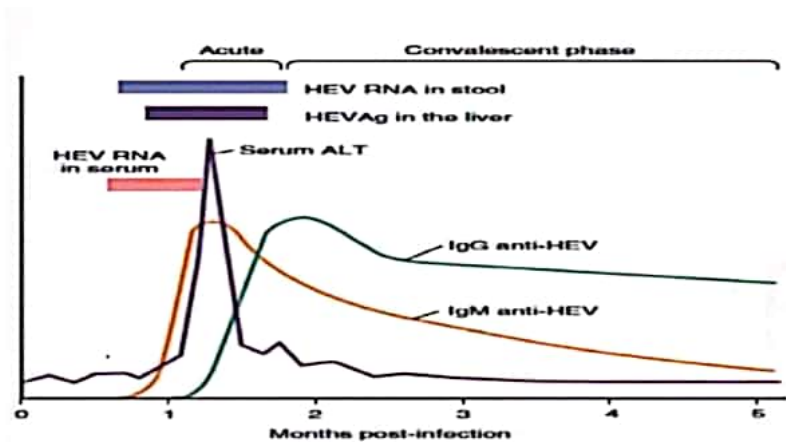
Cardinal points of difference :

1. hep E → Cholestatic phase, hep A → Relapsing Phase

2. vaccine not available for HEV

3. risk of fulminant hepatitis in hepatitis E → 1 - 2%

4. Fulminant hepatitis risk in pregnancy (E) → 20 %



5. Anti HEV IgM → 16 weeks .

6. Clinical recovery → 8 weeks .

• most common cause of acute viral hepatitis in adults → Hepatitis E .

Treatment of acute viral hepatitis

00:22:20

- Jaundice with enzymes extremely high
- Vomiting
- mild hepatomegaly
- Anti HAV or HEV IgM → positive
- Treatment → Hydration Glucose replenishment
 - 10% dextrose (10 gm in 100ml)
 - target- 150gm dextrose per day .
- NO risk for chronicity , cirrhosis , hepatocellular carcinoma .

Acute liver / Hepatic failure

00:00:20

- Encephalopathy +/- coagulopathy occurs within 6 months from the onset of clinical symptoms.
- modified in 6 months → First 7 days → fulminant hyperacute.
- 7-28 days → acute
- 28 days - 6 months → subacute.

Cause :

- viruses → mc cause of acute hepatitis- Hepatitis A(children) & hepatitis E (adults)
mc cause of acute liver failure - Hepatitis E (more incidence)
Risk for fulminant hepatic failure - coinfection of hepatitis D with hepatitis B
B (B ± D)
CMV
HSV
Hemorrhagic virus

rare

E → 1-2%, 20% risk of hepatic failure in pregnancy

D → coinfection with HBV → extremely high risk of hepatic failure (5-20%)

• Drugs :

Dose dependant

- Acetaminophen
- Carbon tetrachloride
- mushroom poisoning

Dose independant idiosyncratic

- INH
- Valproic acid
- Phenytoin
- Carbamazepine
- Propylthiouracil
- Halothane
- Nitrofurantoin

Toxins causing acute liver failure

00:06:10

- Alcohol
- Rat Killer poison (Containing zinc phosphide)
- Metabolic causes : Wilson's disease
Galactosemia
Tyrosinemia
 α_1 antitrypsin deficiency
- Auto immune hepatitis
- Pregnancy related cause → acute fatty liver of pregnancy
→ HELLP
- Vascular causes → Budd Chiari syndrome.
- Metastasis to liver → from breast and lung.

- In Asia and Africa → viral hepatitis (HEV mc in India)
- In Europe → Paracetamol is mc

Acute hepatic failure

00:09:28

Characteristic features:

- **Hepatic encephalopathy** → Cerebral edema
↑ ICP
- Coagulopathy → low platelet count
PT, INR → Elevated.
• Bleeding is rare.
- Renal failure
- Sepsis → Lung related infections. (mc cause of death)
- Electrolyte abnormalities → ↓ Na, ↓ glucose.
- **pulmonary dysfunction** (mc cause of death)
- gastrointestinal bleeding (rarely)
- Hemodynamic abnormalities :
→ Hyperdynamic circulation picture, splanchnic vasodilatation.
→ low peripheral resistance (hypotension) → Increase cardiac output
→ arrhythmias

Management of acute liver failure

00:13:30

- Definitive management- liver transplantation
- prognostic index - **MELD score** → INR
Serum bilirubin
Creatinine

Paracetamol poisoning :

- Toxic dose : **7500mg** (15 tablets)
- Hepatocytes injury - centrilobular hypoxia.
- 1st 24 hours → Nausea and vomiting
- 24-72 hours → Right upper Quadrant pain and tenderness
→ ↑ ALT, ↑ AST, ↑ PT, ↑ Bilirubin
- 72-96 hours → Hepatic necrosis.
Renal dysfunction
Coagulopathy
Encephalopathy
Lactic acidosis.
→ Death occurs.

Symptoms :

- Jaundice not very prominent .
 - Encephalopathy / Cerebral edema .
 - SIRS
 - Renal failure
 - Coagulopathy
- Kings College Hospital Indicators of bad prognosis
- Acute liver failure → paracetamol poisoning .
 - Transplantation required for :
 - PT ↑ or INR > 6.5
 - Encephalopathy
 - serum - creatinine high.
 - pH < 7.25 after 24 hours

management :

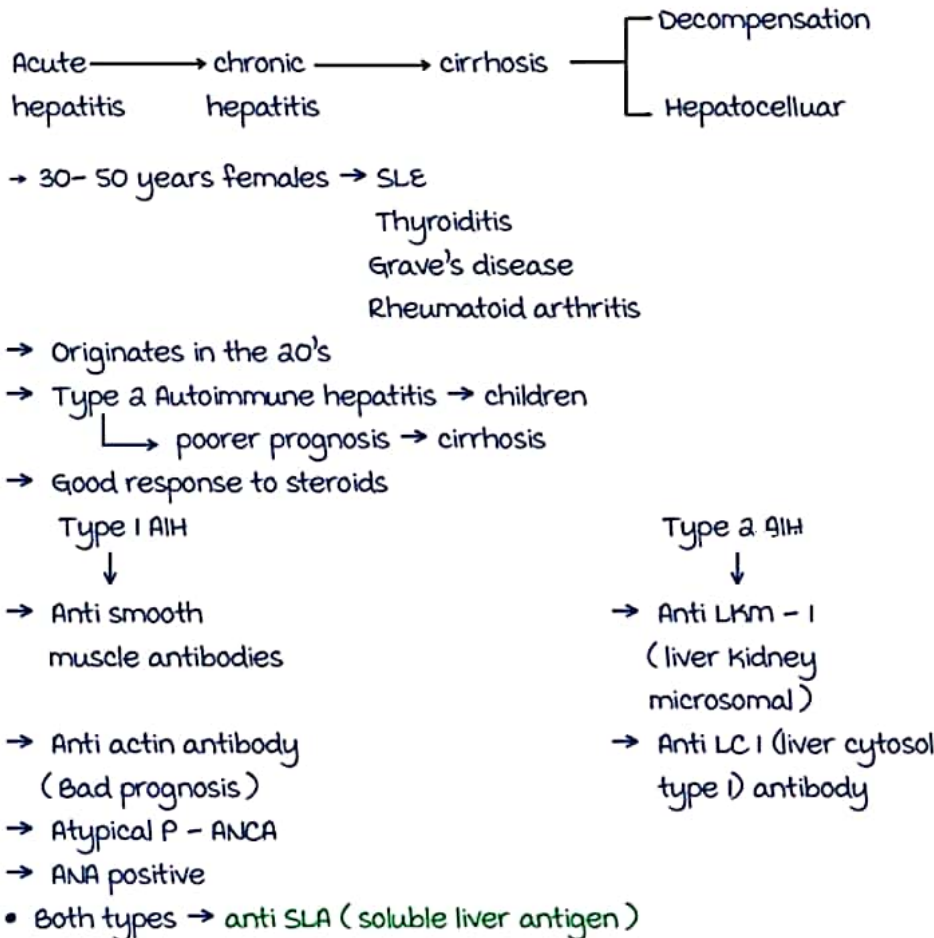
- N - acetyl cysteine → used in drug induced liver injury .
 - ↓
 - - Repletes glutathione
 - Ionotropic
 - Anti inflammatory
 - Given within 15 hours or as early as possible .
 - methionine → alternative drug
 - cerebral perfusion pressure high → > 55 mmHg .
 - N - acetyl cysteine → 300mg /kg . in 3 parts

1 hour - 150mg /kg	→ 200ml 5% dextrose
4 hour - 50 mg /kg	
16 hour - 100mg /kg	

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis

00:00:24



Histology findings :

1. Lymphoplasmacytic infiltrate
2. Interface hepatitis or piecemeal necrosis
3. Emperipolesis
4. Rosette formation

Clinical presentation of autoimmune hepatitis

00:06:38

- Acute hepatitis → chronic hepatitis → cirrhosis
- Cardinal points :
 1. Any acute hepatitis where virus / drug / toxin has been excluded
→ worked up for autoimmune
 2. Any acute hepatitis where jaundice fails to resolve or reappear
(waxing and waning of jaundice)
 3. Any acute hepatitis in a patient with SLE / RA / thyroiditis

4. Any acute hepatitis with polyclonal hypergammaglobulinemia

- Chronic hepatitis :

- Fatigue with LFT → increased ALT / AST
- Hepatomegaly with fatigue in young female
- Cirrhosis
- Autoimmune hepatitis → chances for decompensation less likely

- Decompensated → Jaundice + Splenomegaly
→ Late and less common

- Thyroiditis + Grave's disease + RA

- Asymptomatic / acute / fulminant
rarely rarely

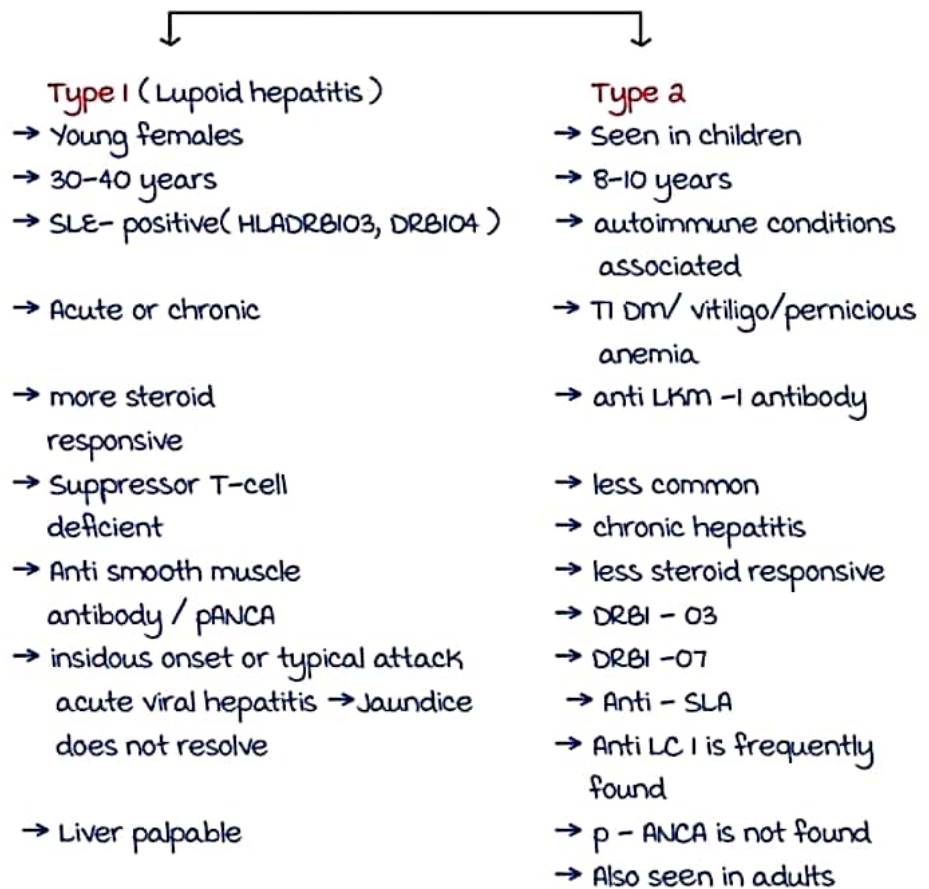
Type

disease

- | | | |
|-------|---|--------------------------|
| LKM-1 | → | AIH type II, Hepatitis C |
| LKM-2 | → | Drug induced hepatitis |
| LKM-3 | → | Hepatitis D |

Type 1 & type 2 hepatitis

00:16:30



Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Treatment of autoimmune hepatitis

00:20:11

- Steroids ± Azathioprine
(Prednisolone)
- Overall prognosis → good if treatment is started before cirrhosis
- S. Bilirubin and enzymes ↓
- Histological remission → to be achieved
- Cirrhotics → transplant
- Recurrence post transplant → 40%

PBC AND PSC

Primary biliary cirrhosis (PBC)

00:00:31

- Now known as primary biliary cholangitis
- Destruction of intrahepatic bile duct (Intralobular)
- Auto immune destruction → T- lymphocyte mediated.
- Females more common than males → 9:1
- 30 - 50 year
- Associated auto immune illnesses .
 - Sjogren syndrome
 - Renal tubular acidosis (RTA)
 - Gall stones
 - Small joint arthritis
- Antibody → anti mitochondrial antibody (AMA)
 - 95% cases , against pyruvate dehydrogenase E_a .
- Differential diagnosis → Intrahepatic cholestasis .
- Chronic progressive auto immune cholestatic disorder .
- No infections
- AMA more than 95 % → IgM . → Presence is good enough for diagnosis .
- Directed against → PDH - E_a
- ALP and GGT → very high .
- Hypercholesterolemia .

Clinical presentation of PBC

00:06:33

- Asymptomatic in 60 % cases
- Routinely diagnosed → ALP ↑ ↑ ↑
- Fatigue is the most common symptom .
- Pruritis → due to accumulation of Lysophosphatidic acid
- melanin deposition → hyperpigmentation .
- Xanthelasmas and Xanthomas → hypercholesterolemia .
- Jaundice in less than 10%
- Hepatomegaly → 25%
- Decompensation occurs late .
- Liver palpable → right upper quadrant pain → 25 %
- Diarrhoea , Steatorrhoea , weight loss → malabsorption
- metabolic bone disease
- Sjogren , RTA , gall stones
- Intrahepatic cholestasis → AMA positive .

Histopathology :

- Biopsy
- Earliest histological changes → **loss of the canals of Hering**
- most important diagnostic clue → **Ductopenia**
 - ↓
 - loss of intrahepatic or intralobular bile duct .
- **Florid duct lesion** with non caseating granuloma

Treatment of primary biliary cholangitis

00:12:24

- Florid duct lesion or chronic non suppurative lesion of inter lobular ducts .
- Drug → preventing progression to cirrhosis
 - **ursodeoxycholic acid (UDCA)**
 - no symptomatic benefits .

New drug → **Farnesoid X receptor antagonist**

↓
Obeticholic acid .

Primary sclerosing cholangitis (PSC)

00:14:12

- Fibrosing destruction with strictures of both intra and extra hepatic bile ducts .
- Seen in males more than females → 2 : 1 .
- Associated with ulcerative colitis (pancolitis)
- 2/3rd of PSC have ulcerative colitis
- 5 % of ulcerative colitis have PSC .
- Increases risk for cholangiocarcinoma .
- Cholestasis (intra + extra hepatic cholestasis)
- Rapidly progresses to cirrhosis
- Very bad prognosis (management - Liver transplantation)
- **AMA negative**
- **Atypical p - ANCA positive**
- Strong HLA association → **DRW 52**
- PSC diagnosed by → **MRCP, preferred over ERCP**
- Stricture and dilatation in between .

Histopathology → Periductal onion skin fibrosis .

- PSC are also asymptomatic .
- Fatigue, pruritis
- Cholangitis is more common
 - Fever, chills, abdominal pain (right upper quadrant pain)
- Jaundice is less than 10 % .

Treatment → Transplantation .

PBC

- Autoimmune condition
- Weak HLA association
- Antibody + T cell mediated
- AMA
- Females
- Sjogren syndrome
- asymptomatic
- AMA → positivity
- ursodeoxycholic acid
- No risk for malignancy
- Ductopenia → florid duct lesion → non caseating granuloma

PSC

- Fibrosing .
- Strong HLA association - DR- W52
- Fibrotic
- AMA negative
- Atypical p - ANCA
- males
- Ulcerative colitis
- asymptomatic
- MRCP
- Liver transplant
- Increase risk of malignancy .
- Onion skin fibrosis .

WILSONS DISEASES

Wilson's disease- etiopathogenesis

00:00:20

- Autosomal recessive.
- 1st manifestation occurs < 20 year.
- Gene : ATP - 7B on chromosome 13q
- ATP 7A gene → menke kinky hair syndrome Characterised by Calcium deficiency

Neurodegenerative condition

→ X linked recessive.

- Copper (Cu) via DMT 1 (divalent metal transporter)

↓ binds to

Intestinal epithelial cells.

↓

metallothioneins

- Copper excreted in bile (90%)
- Circulating copper bound to apoceruloplasmin

↓

Called as Holoceruloplasmin .

- In wilson's disease

(i) copper incorporation into apoceruloplasmin is defective → Rapid ceruloplasmin degradation

(a) Defective biliary excretion of free copper .

- Features :

↑ free copper.

↑ Liver copper

↑ urinary copper

↓ Total copper

↓ serum. ceruloplasmin.

→ Hepatolenticular degeneration occurs

Clinical manifestation

00:07:19

(i) Liver manifestations.

- 1st presentation occurs < 20 years of age.

- Clinical presentation :

- Fatigue, hemolysis .

- Cirrhosis

- Fatty liver.

- Hepatitis, hepatomegaly, cholestasis, can present as any kind of liver disease

- Asymptomatic - but with biochemical abnormality

- Wilsons disease can cause severe form of Jaundice

- Clinical features :

- ↓ Alkaline phosphatase
- ↑ serum AST /ALT
- ↓ cholinesterase.

- (a) Neurological manifestations

- 1st presentation occurs < 10 years of age

- Clinical features.

- (1) Dysarthria (mc)

- (2) Gait abnormalities.

- (3) Dystonia - vacuous smile

- (4) Tremor

- (5) Parkinson like.

- (6) Neuropsychiatric symptoms

- Tremor : wing beating tremor.

- (3) Kayser - fleischer ring. (KF)

- Copper deposition in superior and inferior poles of Descemet membrane.

- Slit lamp examination.

- In neurological wilson disease 95% have KF ring.

- In hepatic wilsons diseases 5% have KF ring

- KF ring also seen in cholestatic conditions.

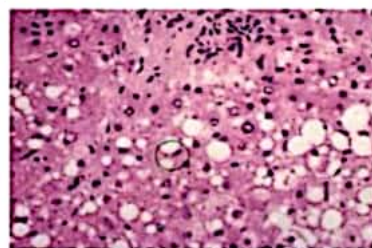
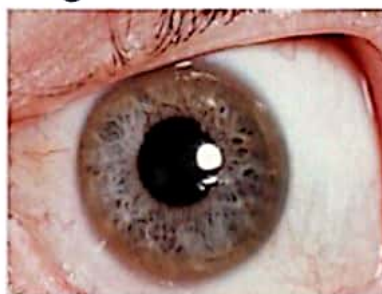
- non specific finding.

- Disappears with therapy.

- Sunflower cataract

- Copper deposition in centre of lens.

- Does not affect vision.



- Other manifestations .

- Endocrine → Hypoparathyroidism
- Renal → Type 2 / proximal renal tubular acidosis.
- Rheumatological → Large joint arthritis .
- GIT → Pancreatitis.
- Amenorrhea, infertility abortion.
- Hematological → Coomb's negative hemolytic anemia .
- Bone disease (India)
- Cardiac : Cardiomyopathy

Diagnosis

- (1) Serum ceruloplasmin

- Synthesised in liver.
- Acute phase reactant protein.
- Normal level 20-40mg /dl
- 6 copper atoms bind to ceruloplasmin .

→ Low serum ceruloplasmin .

< 15 mg / dl → Suggestive of wilsons disease

< 5 mg / dl → Diagnostic of wilsons disease

- Normal values does not exclude diagnosis .
- False low serum ceruloplasmin seen in renal and GI loss of ceruloplasmin .
- False high serum ceruloplasmin seen in
 - Acute inflammation - Positive acute phase reactant
 - Pregnancy .

(a) Total serum copper → Non ceruloplasmin bound copper
(TSC)

+

Ceruloplasmin bound copper

- majority of serum copper are bound to ceruloplasmin

- ↓ Total serum copper and ↓ ceruloplasmin bound copper → wilson's disease .

(3) Urinary copper (24 hrs)

- High 24 hours urinary copper excretion
 - > 100mg suggestive of wilson's disease.
 - 40-100mg → D-penicillamine challenge test



Increase urinary copper → wilson's disease

(4) Hepatic tissue copper - gold standard method

- Copper concentration measured by.
 - (i) Neutron activation analysis
 - Atomic absorption spectrometry
- > 250 mg / g of dry weight - diagnostic

Histopathology :

- Glycogen degeneration → vacuolation
- Fatty changes
- Periportal hepatocytes affected
- macronodular cirrhosis .

Laboratory Measurement	Normal Value	Score (in Points)				
		1	2	3	4	5
Serum bilirubin	12-17 mg/dl	<12	12-15	15-17	17-20	>20
Serum aspartate aminotransferase	10-35 U/L	<10	10-20	20-30	30-40	>40
Prolongation of prothrombin time (sec)	-	4	4.1	4.2	4.3	>4.3

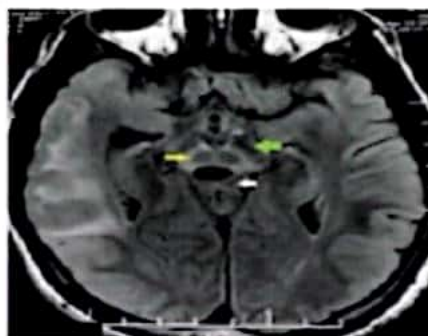
If bilirubin is present, serum bilirubin cannot be used as a measure of liver function and the serum aspartate

Electron microscopy findings and management of wilsons disease

00:25:30

Electron microscopy :

- Tennis Racquet appearance
- Dilation of tips of cristae and widening of intracristal space



Prognostic index

Nazer prognostic index

- Bilirubin
- AST
- Prothrombin time .

Management

DOC : D penicillamine

- 500mg thrice daily
- Along with pyridoxine
- Toxicity : 1 myasthenia gravis
2 Aplastic anemia
3 membranous nephropathy .

2nd DOC : Trientine



given along with Zinc

- in pregnancy DOC : Zinc
In neuro wilson → add tetra thio molybdate .

Zinc

- Induce metallothionein on enterocytes

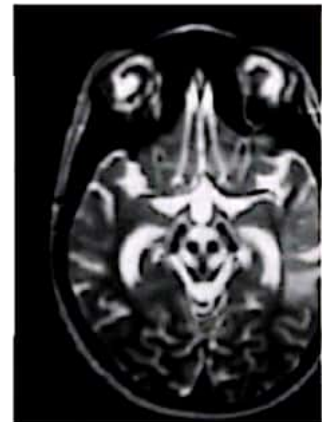


prevents copper exit from enterocytes .

MRI in wilson's disease

T₂ hyperintensities .

- Face of giant panda sign
- Superior colliculus - low intensity (Chin and mouth)
- tegmentum - ↑ intensity (eyes)
- Pars reticulata - preservation of signal intensity (ears)



Bright claustrum sign

Thin rim of T₂ hyperintensity in claustrum

In pons

- a. Hyperintensity of pons
- b. Hyperintensity bisected by line



c. Trisected hyperintensity

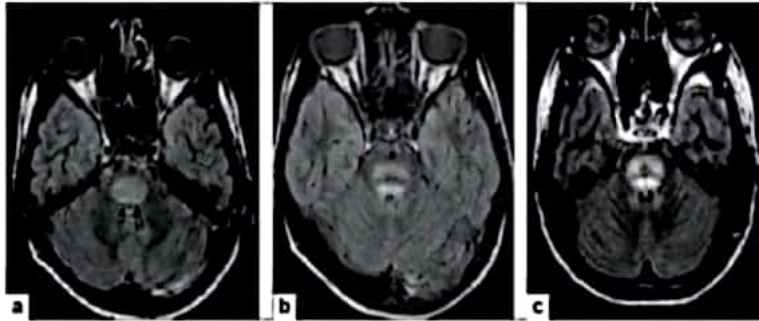


“mercedes Benz sign”

or

“Trident sign”

Brain Stem changes: CPM like

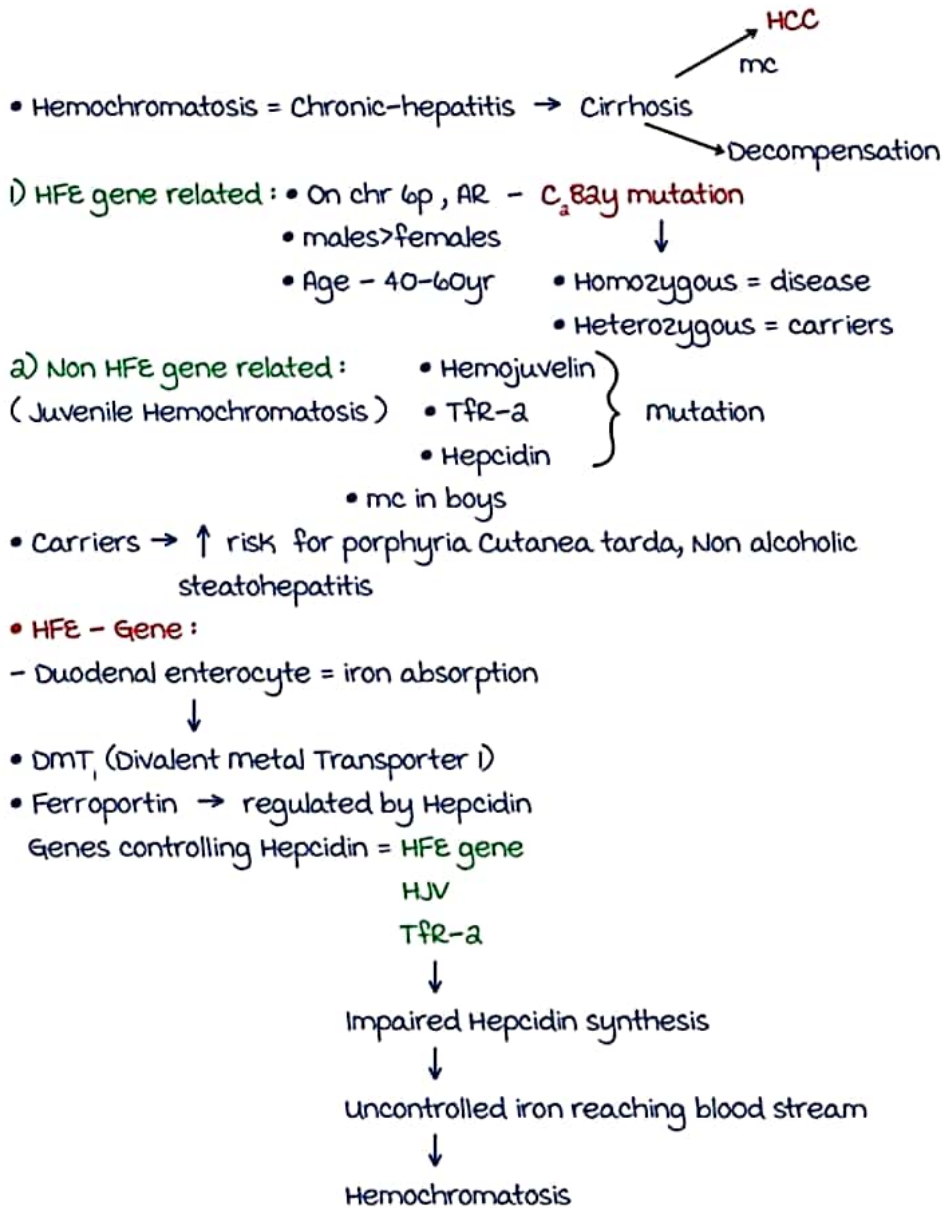


- Classical: Hyperintensity of whole of the central pons sparing a peripheral rim;
- Bisected pontine signal change by a horizontal line and;
- Trisected: Pontine hyperintensity trisected by a hypointense line like 'Mercedes Benz' sign

HEMOCHROMATOSIS

Hereditary hemochromatosis

00:00:21



Disease course : Hemochromatosis

00:07:24

- Chronic hepatitis is the early stage
 - Liver → • Periportal hepatocytes (iron accumulation site)
 - mixed / macronodular (cirrhosis - mostly asymptomatic)
 - Hepatomegaly (AST & ALT < 150, ALT > AST) fatigue
 - Skin → Bronzing/metallic/slate grey hyperpigmentation
 [Fore arms, Dorsum of hand, Neck]
 - Pancreas → Pancreatic diabetes [Type 3c]

- Joint → Small joint Non erosive , Non inflammatory arthropathy ~~~~~→ pseudogout (chondrocalcinosis)
- Gonads → Hypogonadism [hypogonadotropic type]
- Heart → Diastolic dysfunction (dilated cardiomyopathy), Conduction blocks.



Arthropathy



- High mucosal absorption (> 4g/day)
- Hepcidin responds to signal mediated by HFE/TfR2/Hemojuvelin

↓
(N) Individual

Diagnosis : hemochromatosis

00:14:09

- Screening test : Iron status.

- Serum ferritin ~~~~~→ ↑↑

- % Saturation of transferrin (PSAT) = $\frac{S.Iron}{TIBC} \times 100$ } cut off → 45%

Best method : S. ferritin + PSAT

↑↑ S. ferritin (> 1000ng/ml)

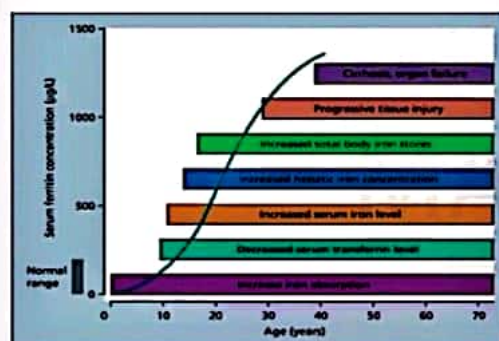


- Baa prognosis.

S.Iron → Iron bound to transferrin in circulation

TIBC - Total Iron Binding capacity
S.transferrin Level.

Natural history of HH



Confirmatory test : C282Y mutation

- Alcohol ↑ risk for cirrhosis in hemochromatosis

Representative Iron Values in Normal Subjects, Patients with Hemochromatosis, and Patients with Alcoholic Liver Disease

Determination	Normal	Symptomatic Hemochromatosis	Homozygotes with Early, Asymptomatic Hemochromatosis	Heterozygotes	Alcoholic Liver Disease
Plasma iron, mmol/L (mg/dL)	9-27 (50-150)	32-54 (180-300)	Usually elevated	Elevated or normal	Often elevated
Total iron-binding capacity, mmol/L (mg/dL)	45-66 (250-370)	36-54 (200-300)	36-54 (200-300)	Elevated or normal	45-66 (250-370)
Transferrin saturation, percent	22-46	50-100	50-100	Normal or elevated	27-60
Serum ferritin, mg/L		900-6000	200-500	Usually <500	10-500
Men	20-250				
Women	15-150				
Liver iron, mg/g dry wt	300-1400	6000-18,000	2000-4000	300-3000	300-2000
Hepatic iron index	<1.0	>2	1.5-2	<2	<2

Treatment : hemochromatosis

00:17:34

- TOC - Phlebotomy [if cirrhosis $\oplus$ $\rightarrow$ efficacy $\downarrow$]

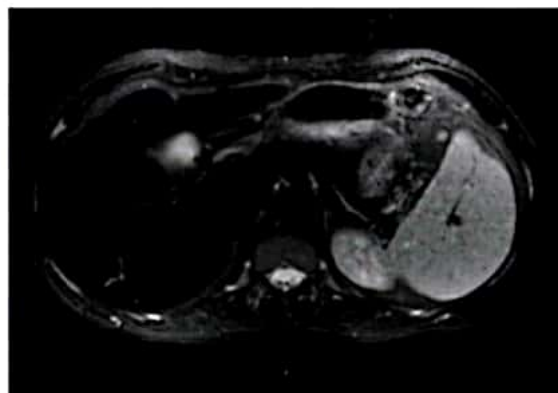
$\downarrow$ Cannot reverse joint & Gonads changes

Remove : 1 unit of whole blood weekly

500ml of blood
 $\downarrow$
250mg of iron

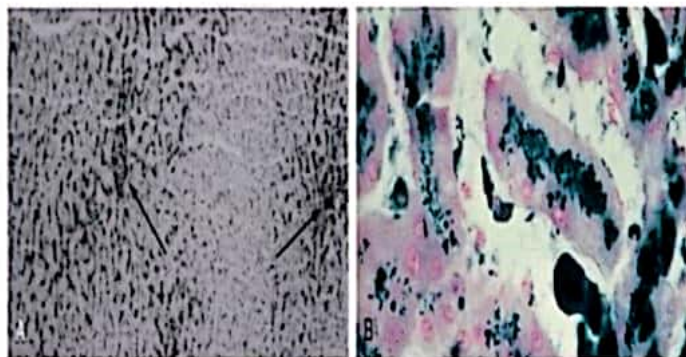
when S. Ferritin < 50ng/ml $\rightarrow$ once monthly phlebotomy

- If phlebotomy is not well tolerated $\rightarrow$ s/c Desferrioxamine
Daily for 5 days a week
- Liver transplant is done when Cirrhosis & decompensation sets in
 - $\uparrow$ Risk of HCC - post transplant



Classification of Iron Overload States	
Hereditary Hemochromatosis	
Hemochromatosis, HFE-related (type 1)	
C282Y homozygosity	
C282Y/H63D compound heterozygosity	
Hemochromatosis, non-HFE-related	
Juvenile hemochromatosis (type 2A) (hemojuvelin mutations)	
Juvenile hemochromatosis (type 2B) (hepcidin mutation)	
Mutated transferrin receptor 2, TFR2 (type 3)	
Mutated ferroportin 1 gene, SLC11A3 (type 4)	
Acquired Iron Overload	
Iron-loading anemias	Chronic liver disease
Thalassemia major	Hepatitis C
Sideroblastic anemia	Alcoholic cirrhosis, especially when advanced
Chronic hemolytic anemias	Nonalcoholic steatohepatitis
Transfusional and parenteral iron overload	Porphyria cutanea tarda
Dietary iron overload	Dysmetabolic iron overload syndrome
	Post-portacaval shunting

- Prussian Blue Staining used for Iron.



NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

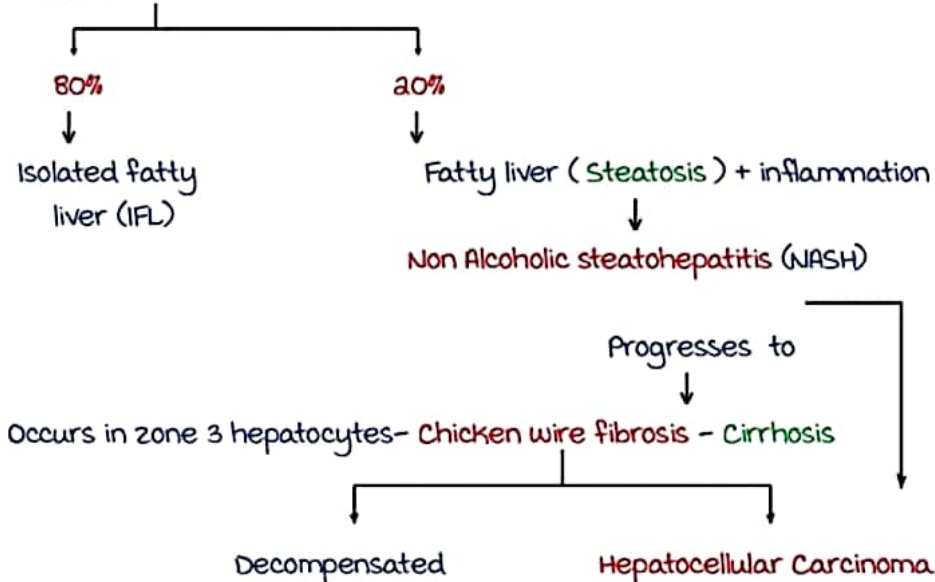
Definition

00:01:10

- NAFLD - Fat accumulation in more than 5% of hepatocytes (macrovascular steatosis)

Alcohol intake <30 g/d males or <20 g/d in females

- In NAFLD



Difference between IFL and NASH, two hit hypothesis

00:06:50

- For difference between IFL and NASH

↓
Liver biopsy - degree of Steatosis
- degree of Lobular inflammation
- Ballooning of hepatocytes

In NASH there will be - more degree of Steatosis,
more degree of Lobular inflammation
more ballooning of hepatocytes

Steatosis	
5%	1
5%-33%	2
33%-66%	3
Ballooning	
None	0
Few	1
Many	2
Lobular Inflammation	
Mild	1
Moderate	2
Severe	3
Total Score	
0-2	Likely not NASH
3-4	Intermediate
5-8	Likely NASH

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Active space

Two hit hypothesis

- Risk factors for NAFLD - m.c - Starvation

Obesity

Sedentary lifestyle

metabolic syndrome

Insulin resistance

Polycystic ovarian syndrome

- In NAFLD - in the presence of oxidative stress/ mitochondrial dysfunction/ Gut dysbiosis or endotoxins



Can develop NASH

Causes- of NAFLD, NASH

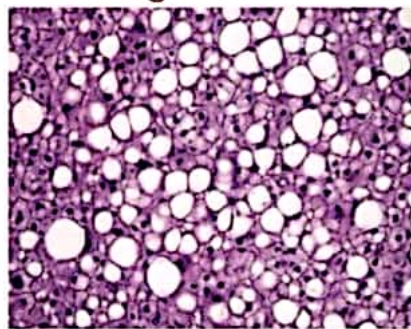
00:12:02

Drugs:

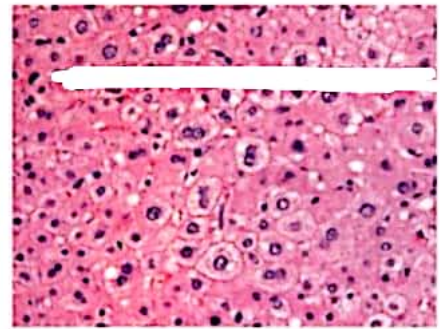
- 1) Bleomycin - m.c
- 2) Tetracycline
- 3) Azacitidine
- 4) L- asparaginase
- 5) Estrogen and steroids
- 6) valproate
- 7) Nitrofurantoin
- 8) Amiodarone

metals

- Barium
- Chromium
- mercury



Fatty liver



Ballooning of hepatocytes

Liver enzymes in NASH, IFL

00:16:25

- If Liver enzymes (AST, ALT) - Normal
+ Fatty liver } → likely to be IFL
- If liver enzymes (AST, ALT) - $< 150 \mu\text{I}$
+ Fatty liver } → NASH
- If Liver enzymes (AST, ALT) - $< 150 \mu\text{I}$ but $\text{AST} > \text{ALT}$
↓
likely to be NASH + cirrhosis
↓
Should definitely perform a fibroscan
- Other signs - Hepatomegaly
Right upper quadrant pain

Associations of NASH

- Obstructive sleep apnea syndrome
- Polycystic ovarian Syndrome
- Coronary artery disease
- Colonic adenomas
- Hypothyroidism
- Vitamin D deficiency

Symptoms of NASH, NAFLD

00:21:03

- Common symptoms - none
- Common sign - hepatomegaly
- Uncommon symptoms - vague right upper quadrant pain
Fatigue
malaise
- Uncommon signs - Splenomegaly .
Spider angioma
Palmar erythema
Ascites
- Low adiponectin levels + Leptin resistance

Diagnosis -

- Fibro Scan - **Transient elastography**
- In NASH - **Serum ferritin levels are high**
- Blood markers of fibrosis - **Cytokeratin 18**
terminal peptide of procollagen 3

Management of NASH, NAFLD

00:24:59

- NAFLD - Active exercise + weight reduction
- NASH - Weight reduction
D.O.C. Vitamin E: 800-1000 IU/day
Pioglitazone, Pantoxiphylline
Regular Coffee consumption
Omega 3 fatty acid consumption

TABLE 87-3 Treatment Options for Patients with Nonsalcoholic Fatty Liver Disease (NAFLD) and Nonsalcoholic Steatohepatitis (NASH)		
Option	Effect	Comments
Diet		
Moderate calorie restriction; aim to reduce daily calories by 500-750 kcal and achieve weight loss of 7%-10%	Improves most histopathologic features of NASH	Data are lacking for fibrosis improvement; only ~40% of patients were able to achieve this goal in clinical trials
Eliminate or significantly reduce saturated fatty acids and high-fructose corn syrup from diet	Fructose increases lipogenesis via activation of pyruvate dehydrogenase and transcriptional activation of sterol regulatory element-binding protein 1. May decrease hepatic elastosis; improves TG levels	Prospective trials demonstrating biochemical and histologic benefit of fructose reduction are lacking, although fructose consumption is a risk factor for NAFLD. The optimal dose is unclear, but some benefit may be seen with ~1 g daily; treatment for 1 year or longer is associated with reduced risk of cardiovascular death, sudden cardiac death, all-cause mortality, and nonfatal cardiac events
Consider omega-3 fatty acid supplementation		Optimal amount is unclear, but data suggest at least 2 cups daily
Consider regular coffee consumption, 2-3 cups daily	Decreases risk of hepatic fibrosis	
Exercise		
Moderate exercise 4-5 times weekly for 30-45 minutes each time	Improves insulin resistance, liver enzyme levels, and steatosis by imaging	No studies have assessed the effect on NASH histopathology; weight loss is not expected without associated dietary modification
Resistance training 3 times weekly; total exercise time ~45 minutes/week	Improves insulin resistance and steatosis by imaging modestly	Likely best combined with aerobic exercise and diet
Pharmacotherapy		
Vitamin E 800-1000 IU daily	Improves NASH when used for 2 years; no improvement in fibrosis	Validation studies in diabetics and various ethnic groups are needed to confirm a benefit; may increase risk of prostate cancer
Pioglitazone 30-45 mg daily	Improves NASH when used for 6 months to 2 years; may improve fibrosis	Expect a 4-kg weight gain; possible increased risk of heart failure, and osteoporosis; not approved by FDA for NASH treatment; limit use to patients with stage 2 fibrosis or greater who have failed to improve with dietary measures and exercise
Pantoxiphylline 400 mg three times daily Statins	Improves NASH and fibrosis Limited data on histopathology	Small pilot trial data only Safe in patients with NAFLD; reduces risk of cardiovascular disease

ALCOHOLIC LIVER DISEASE

- mcc of Cirrhosis in India → **Alcoholic Liver Disease [ALD]**
- Cirrhogenic dose of Alcohol → ♂ = 40-80g/ day
♀ = 20-40g/ day

Alcohol Content of Various Beverages					
Beverage	Approximate Alcohol Content	Serving Size	Amount of Alcohol	Daily Intake Needed to Exceed Threshold for Alcoholic Liver Disease*	
				Men	Women
Beer	5%	12 oz	14.02 g	3-6 cans	1.5-3 cans
Wine	12%	5 oz	14.02 g	3-6 glasses	1.5-3 glasses
Hard liquor	40%	1.5 oz	14.02 g	3-6 drinks	1.5-3 drinks

*Alcohol intake of 40-80 g/day for men and 20-40 g/day for women for 10 years.

Standard drink (12 gms abs.alcohol)

Drink Equivalents



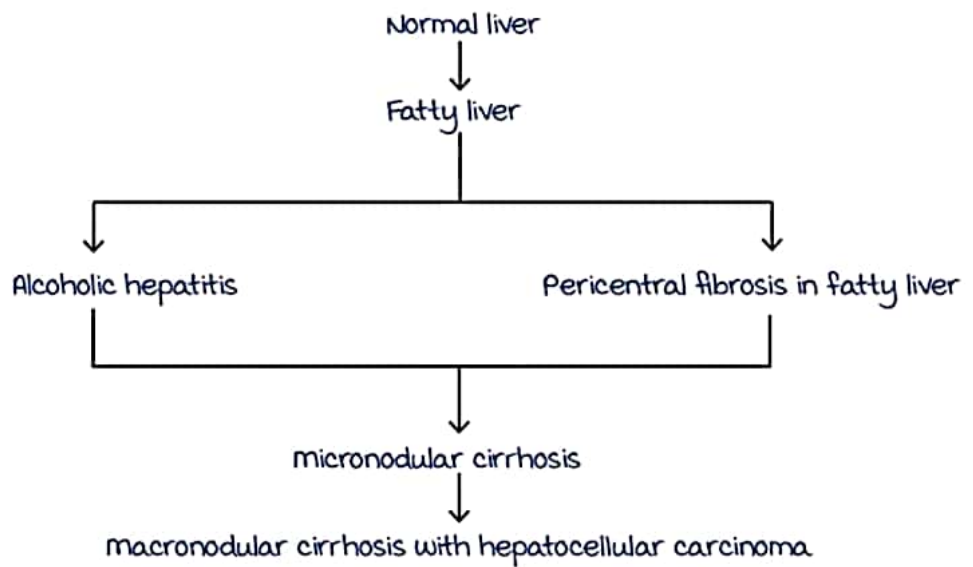
12 ounces 4 ounces 1 ounces

One beer wine hard liquor

1 ounce = 30 ml

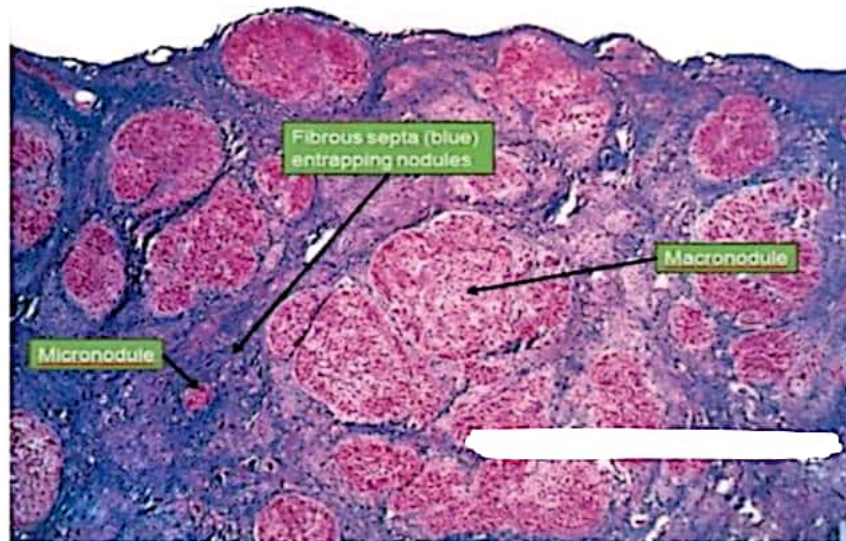
Small peg - 30ml
large peg - 60ml

Course of Disease



Cirrhosis starts in - Zone 3

Alcoholic hepatitis → 70% mortality



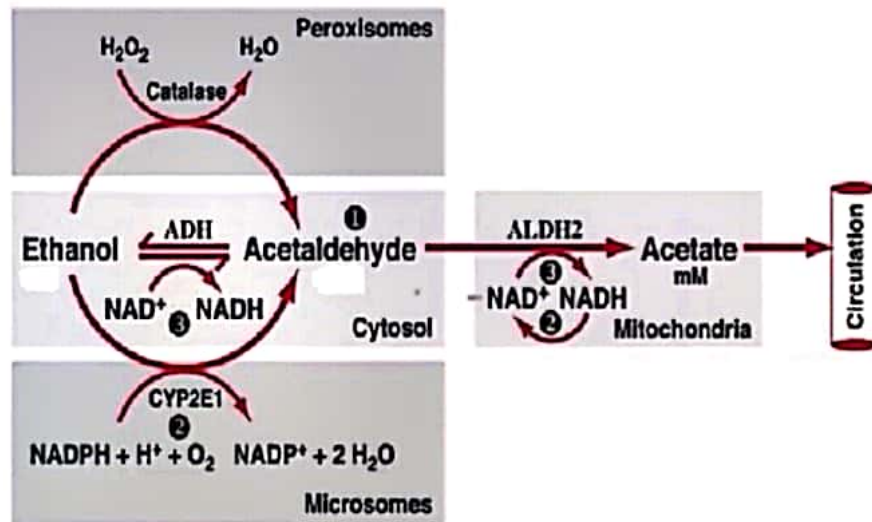
macro nodule → > 3mm

micro nodule → < 3mm

Alcohol metabolism

00:08:28

- Alcohol dehydrogenase (ADH)
 - Cytochrome P_a E₁ (CYP_a E₁)
 - Catalase
- } Product : Acetaldehyde



Acetaldehyde : - depletes Glutathione
 - $\uparrow$ reactive O_2 species
 - Adducts are formed in liver
 - $\uparrow$ $NADH/NAD$ ratio

In cirrhosis $\rightarrow$ Oxidative stress $\uparrow \rightarrow$ mitochondrial dysfunction

Fibrosis $\leftarrow$ Hepatocyte hypoxia
 (Zone 3 - centrilobular zone)

Best serum marker for ALD : Carbohydrate deficient Transferrin

Cause for thrombosis in ALD :

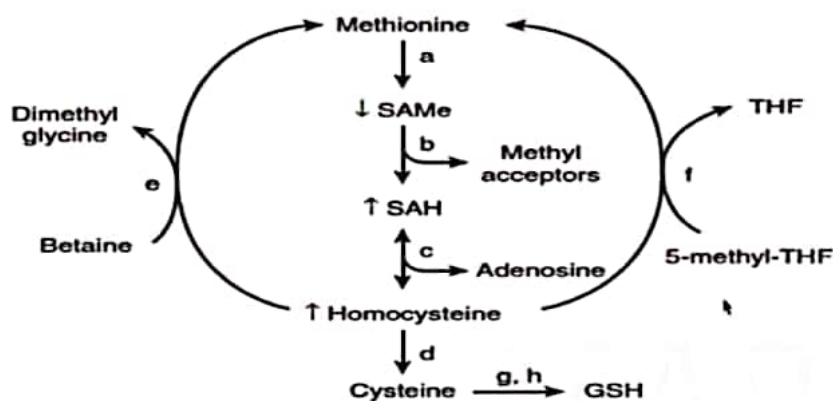


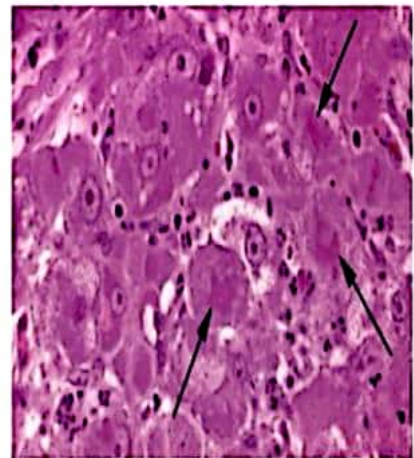
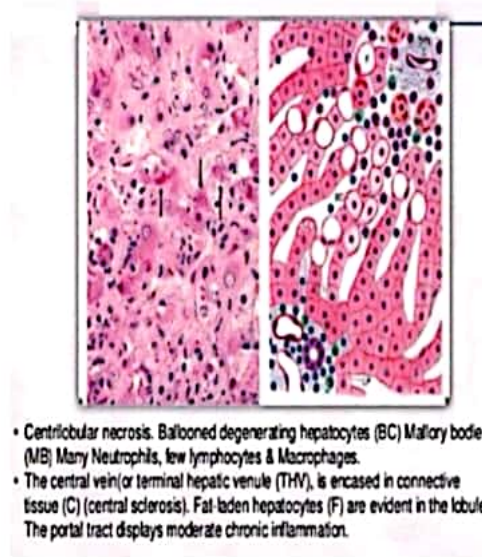
FIGURE 86-3. Hepatic methionine metabolism. Chronic alcohol consumption causes S-adenosylmethionine (SAME) deficiency and an increase in S-adenosylhomocysteine (SAH) and homocysteine levels. a, methionine adenosyltransferase; b, enzymes involved in transmethylation reactions, including phosphatidylethanolamine N-methyltransferase; c, SAH hydrolase; d, cystathionine B-synthase; e, betaine-homocysteine methyltransferase; f, methionine synthetase; g, glutamate-cysteine synthetase; h, glutathione (GSH) synthetase; THF, tetrahydrofolate; $\uparrow$, $\downarrow$, effects of alcohol.

Increase in S-adenosyl homocysteine $\rightarrow$ thrombosis

- MC after binge drinking
- Presents similar to acute hepatitis
- Liver inflammation ⊕
- mostly neutrophil mediated
- ↑ mortality (70%) →
 - Encephalopathy
 - Coagulopathy
- $AST > ALT$; $\frac{AST}{ALT} > 3:1$
- $AST \& ALT \rightarrow < 300 \text{ u/l}$
- macrocytic Anemia/ megaloblastic Anemia → due to ↓ Thiamine
- $mcv \uparrow$, $TC \uparrow$, $PT \uparrow$, $Sr. \text{Albumin} \downarrow$ (-ve acute phase reactant)

Alcoholic Hepatitis : Histopathology

00:16:59

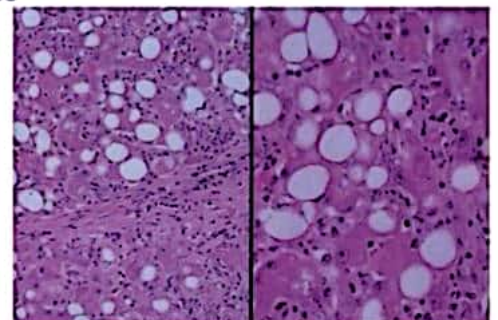


Eosinophilic mallory body

- Neutrophil mediated inflammation
- Ballooning degeneration (Zone 3)
- mallory body → made of Intermediate filaments (Cytokeratin 8/18)

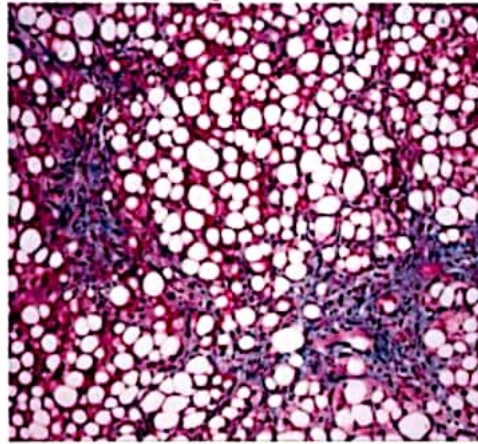
Other Conditions for mallory Denk bodies :

- Wilson's disease
- Indian childhood cirrhosis
- NASH
- Cholestasis
- Alcohol / $\alpha 1$ Antitrypsin deficiency
- Primary Biliary Cirrhosis
- HCC



- Hepatitis C → Chronic Hepatitis with fatty liver

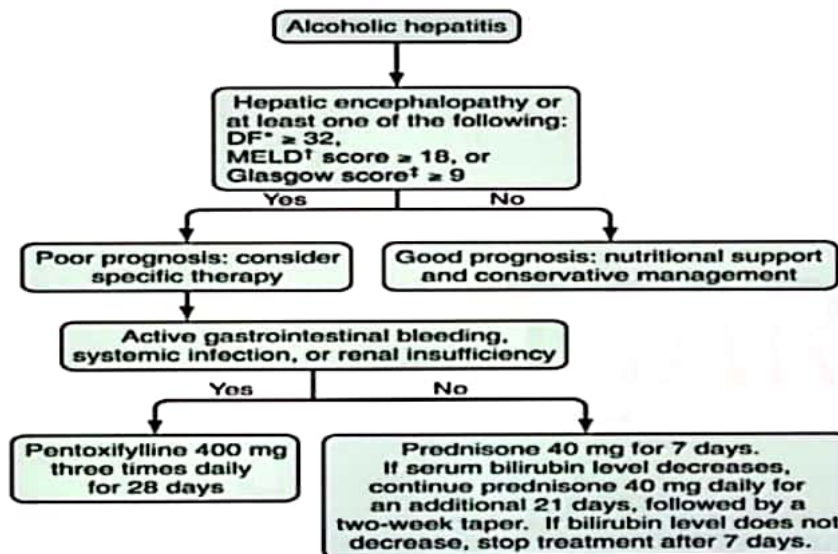
Fatty liver in ALD :



Microvesicular Steatosis

ALD : management

00:19:55



Severity markers :

- Hepato-encephalopathy
- MELD Score > 18
- Glasgow score > 9
- Discriminant fraction ≥ 32

Bad prognosis

$$DF = 4.6 (PT_p - PT_c) + \text{Serum bilirubin}$$

- if $DF < 32 \rightarrow$ Conservative management

PT_p = Prothrombin time of Patient
 PT_c = Prothrombin time of Control

- if $DF \geq 32 \rightarrow$ Bad prognosis = Start Steroid for 1 week (Prednisolone) (or)
 Active GI bleed $\rightarrow$ Pentoxifylline 400mg TID

- Portal Hypertension in absence of cirrhosis → Alcoholic hepatitis.

Acetaminophen intake :

In chronic alcoholic liver disease



Acetaminophen poisoning

- ALT & AST > 1000
- AST > ALT

micronodular Cirrhosis : Causes - • Alcohol

- Biliary cirrhosis
- Indian childhood Cirrhosis
- Budd Chiari Syndrome
- Cystic fibrosis

Hemochromatosis - mixed cirrhosis

microvesicular steatosis : Causes : Pregnancy (AFLP)

Reyes syndrome

Eclampsia

Tetracycline

Valproate

Jamaican Sleeping sickness

Alcohol

Acid lipase deficiency

NASH & Chronic hepatitis - macrovesicular Steatosis

Reyes Syndrome - Swollen mitochondria ↓ in numbers

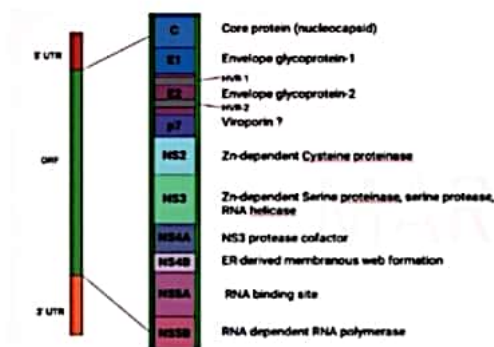
Nutmeg liver - Chronic venous Congestion

HEPATITIS C

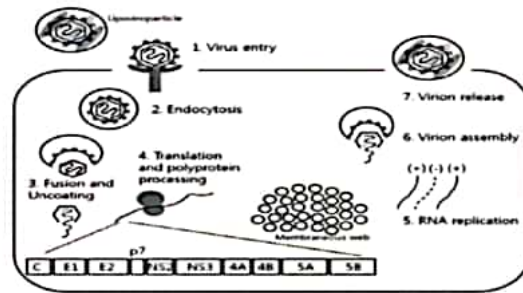
Hepatitis C virus - structure

00:00:50

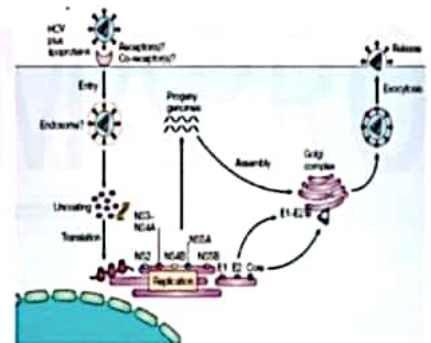
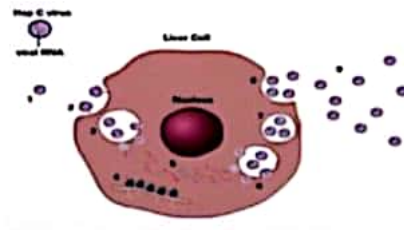
- Single stranded RNA
- Flaviviridae family → Hepacivirus
- Positive sense single stranded RNA
- 9.7 Kb in length
- Structural proteins :- Core protein
Envelope protein E_1
Envelope protein E_2
- Non structural proteins :- NS_3 and NS_3 , NS_{4R} , NS_{4B} , NS_{5R} , NS_{5B}



- Host signal peptidase will cleave the structural proteins from non structural proteins
- E_2 → most variable region of HCV genome
- Directly acting antiviral drugs → NS_3 , NS_{5R} , NS_{5B}
 - inhibitors : NS_3 → evir
 - NS_{5A} → avir
 - NS_{5B} → uvir
- Core protein forms viral nucleocapsid
- E1 and E2 proteins for viral assembly
 P_1 → ion channels for viral release
- NS3 is the serine protease / function as serine protease is enhanced by association with NS4A
- NS5A - RNA binding site within replication complex
- NS5B - is the RNA dependent RNA polymerase



1. HCV Virus infects human
2. Binding to unidentified cell surface receptor and internalization in liver cell
3. Cytoplasmic release and uncoating of RNA genome
4. Translation and polyprotein processing by cellular and viral proteases
5. RNA replication
6. Packaging and assembly
7. Virion maturation
8. and 9. Release from host cell



→ 6 - genotypes

Epidemiology :

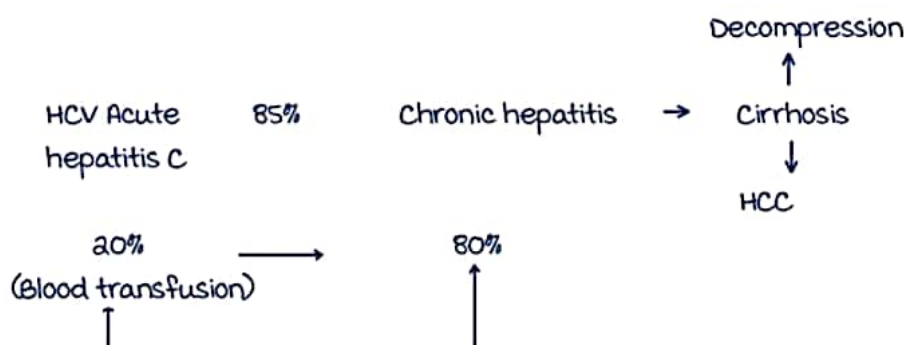
- Punjab in India has highest prevalence
- Estimated prevalence in India → 0.5 - 1.5%
- Higher prevalence in Punjab → 5.2% (3.2%)
- **Geno 3** - Commonest genotype in India → most prone for **Cirrhosis**
- **Geno 1** - commonest worldwide
- No vaccines

Transmission :

- Blood transfusion incidence :

Hep B	Hep C
→ 1 case for every 2 lakh units	→ 1 case for every 18 lakh units
- most common mode of transfusion of hepatitis C virus
 - i.v. drug abusers (sharing needles)

- Transfusion hepatitis → CMV or EBV or HCV
- Chronic hemodialysis patients - needle prick → 1.8 - 6%
- efficient percutaneous transmission
- Transfusion related → 4% only (acute HCV)
- IVDU → 48 to 90%
- Chronic hemodialysis
- Needle stick in health-care workers Seroconversion → 1.8 - 6%
- Rare form of transmission :
 - Perinatal → 5 - 7%
 - Vaginal delivery → no risk
 - Breast feeding → negligible, advised to feed
- Percutaneous - i.v. Drug users → 1.8 - 6%

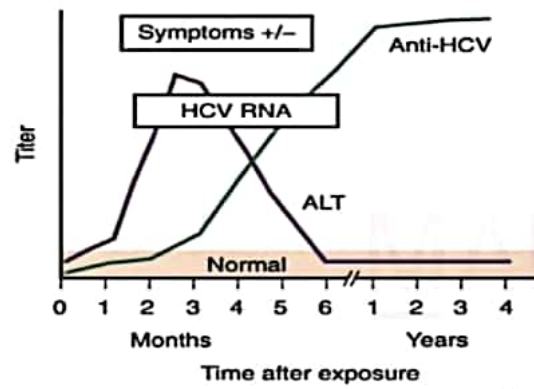


Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Acute Hepatitis C

00:17:53

- Acute HCV → 20% of cases
- 85% → chronicity after acute hepatitis C
- Incubation period → 50 days
- Non specific manifestations
- Anicteric hepatitis
- Jaundice → 10 - 20%
- Clinical features → Nausea, vomiting, headache
- ALT, AST → very high
- Risk for fulminant hepatic failure → 0.5 - 1%
- Rare in clinical practice → majority asymptomatic
- 20% risk for Cirrhosis in patients followed up for 20 years



- Anti HCV → positive
- HCV RNA → positive
- 6 months → 85% HCV RNA positive → chronic HCV
→ 15% HCV RNA undetectable → recovered

Symptomatic patients :

- Vomiting, Enzymes -high
- Acute HCV
 - HCV RNA → positive
 - Anti HCV → positive

Screening :

- | | |
|----------------------|------------------------|
| → Anti HCV positive | → false positive |
| - Chronic HCV | or recovered acute HCV |
| ↓ | ↓ |
| Hcv RNA → detectable | HCV RNA → undetectable |

In chronic HCV

- ALT / AST enzyme are of no value
- variable and fluctuating

Chronic Hepatitis C

00:26:23

- Screening → anti HCV → positive
- HCV RNA detectable (enzymes have no value)
- Patient with fatigue with variable enzymes, arthralgias, Paraesthesias, myalgias, pruritis, sicca syndrome
- Extrahepatic manifestations
- Cirrhosis and its complications

Extra-hepatic manifestations :

- Essential mixed Cryoglobulinemia

- Lichen planus
- Porphyria cutanea tarda
- Sjogren syndrome → marginal zone B-cell lymphoma
- Auto immune thyroiditis
- membrano proliferative glomerulo-nephrities (MPGN)
- Diabetes mellitus

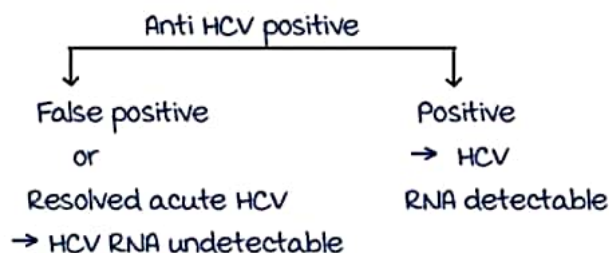
- Anti-LKMI → chronic HCV
 - Auto immune hepatitis type - 2
- Anti-LKIIa → Drug
- Anti-LKIII → chronic hepatitis D

- Cryoglobulinemia → fatigue + arthritis + confluent
Purpura + neuropathy + MPGN | Raynaud's

Diagnosis of Hepatitis C

00:33:10

- Indirect
 - EIA → detects antibodies
 - Latest EIA 3 (as early as 7-8 weeks)
 - Negative → if no hemodialysis, HIV
 - Anti HCV → positive



- Anti HCV negative
 - CKD patient on dialysis go for HCV RNA

management :-

Acute HCV	Chronic HCV	Cirrhosis	Decompensation
	↓		
	99%	75-80%	55-60%
	SVR	SVR	SVR

- SVR → Sustained Viral Response
- HCV RNA → undetectable after 12 weeks

→ Directly acting anti viral drugs

→ Pangenotypic drugs :

NSSA inhibitor with NSSB inhibitor x 12 weeks

- Velpatasavir + Sofosbuvir
(100 mg daily) (400 mg daily)

Decompensated cirrhosis → add Ribavirin

NSSA

NSSB

- | | |
|-----------------------------|------------------------------|
| - AVir (++) ← Potency | - wvir |
| - Low barrier to resistance | - high barrier to resistance |

- WHO recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older irrespective of disease stage.
- WHO recommends the use of pan-gene typic DAA regimens for the treatment of persons with chronic HCV infection aged 18 years and above.

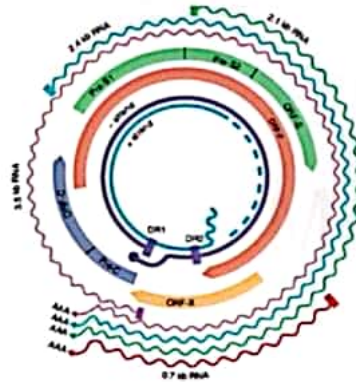
HEPATITIS B

Hepatitis B

00:00:32

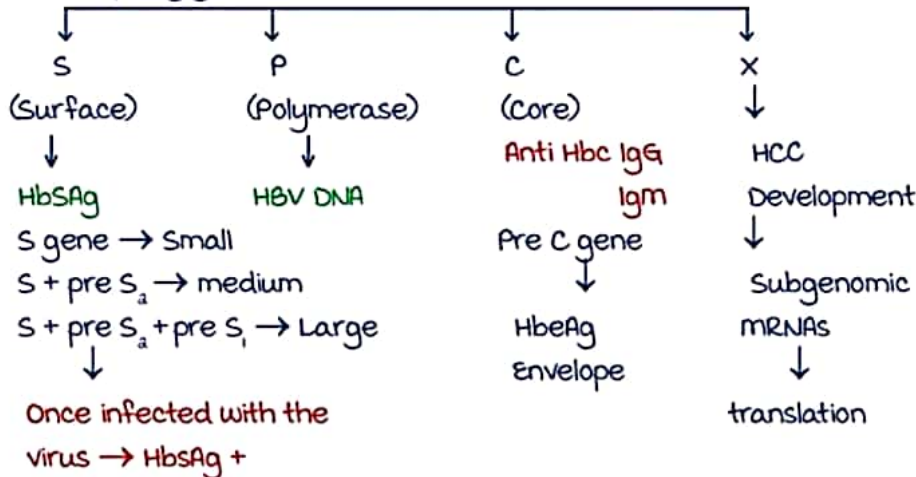
Hepatitis B Virus

- DNA virus
- Hepadnaviridae
- Partially double stranded



42nm Dane particle

4 overlapping genes



S-gene mutation ('a' gene)

Escape mutant

HbsAg -, HBV DNA +

↓
Occult HepB infection

	Acute Hep B	Chronic Hep B
HbsAg	+ ve	- ve
IgG	IgG - ve	+ ve IgG
anti Hbc Igm →	IgG + ve (best)	- ve Igm
HbeAg (Qualitative factor)	±	±

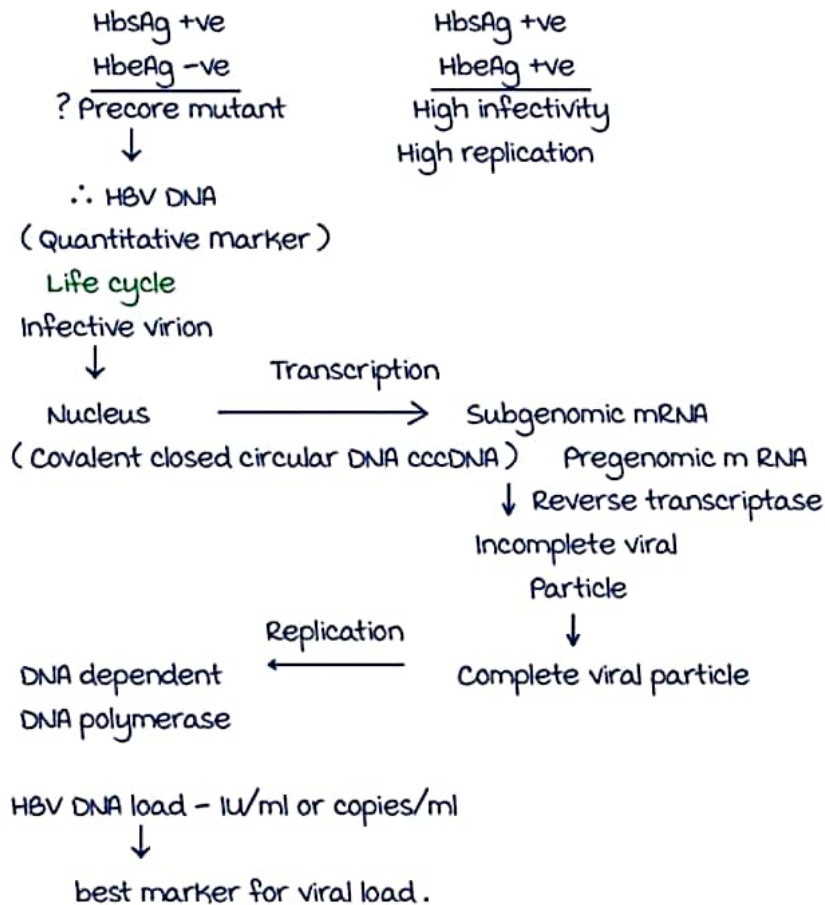
Precore / Basal core mutation



Can't express HbeAg

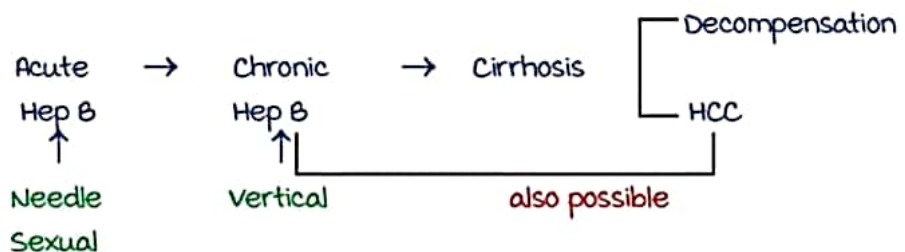
Problems of Ag - Ab of HBV

00:10:45



Natural history of HBV

00:18:40



Facts

1. cccDNA - Pregenomic mRNA is not under the control of P gene.
2. Core particles interacts with S protein to initiate viral assembly in the ER.

10 genotypes - Type A (mc)

100 times infectious as HIV

10 times infectious as HCV



All body fluids except stool



Prick 6%-30%

mother → child 90/10 risk

HbsAg + ve HbeAg - ve - 10%

HbsAg + ve HbeAg + ve - 90%

1 in 2,00,000 units of blood transfused (infected)

Percutaneous- 6 to 30%

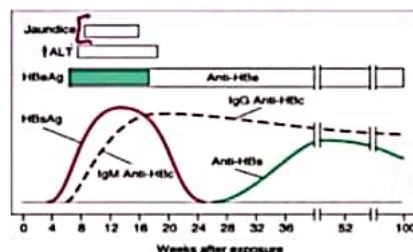
Chronic { vertical 100%
Any other mode 5%

Interpretation of HBV serology

00:26:35

1. Acute Hepatitis B (incubation - 60 days)

- HbsAg +ve
- anti Hbc IgM +ve
- +/- Hb E Ag



2.

after 6 months

95% recovery

HbsAg = -ve

Anti Hbc Ag IgG = +ve

Anti Hbs = +ve

5% - Chronic Hepatitis B

HbsAg = +ve

Anti Hbc IgG = +ve

Hbe Ag = +ve

3. HbsAg

Anti Hbc IgG = +ve

Anti Hbe = +ve

Hbe Ag = -ve

Low infectivity/low replication

HBV DNA < 2,000 IU/ml

Pre-core mutant

HBV DNA < 2,000 IU/ml

4. Hb SAg +ve : 2 genotypes
Anti HbsAg + ve

5. anti HbC IgM +ve : Acute Hepatitis B

6. anti HbC Ig + ve :
┌ Remote infection (significant if going for transplant)
└ False positive

7. anti HbsAg + ve. : Vaccination

Precore / basal core mutants

00:41:32

- Unable to secrete HbeAg
 - Bad prognosis
- ↓
- Core promoter mutation
- ↓
- HCC

Hep A - 100% recovery

Hep B - 95%

Hep C and Chronicity - 85% Chronic

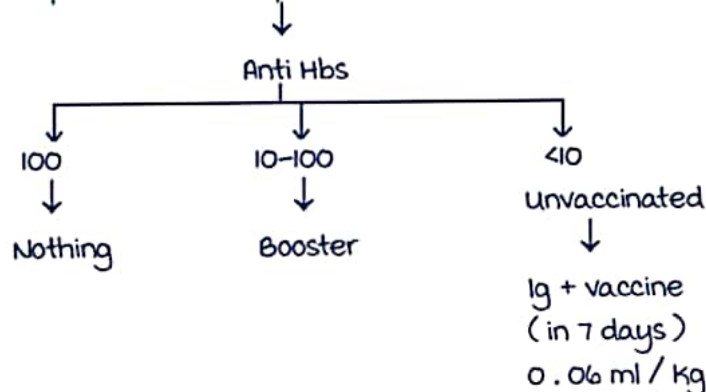
Hep E - 100% recovery

Perinatal transmission (mother HbsAg +ve)

↓

Hep B immunoglobulin(Ig) soon after birth 0.5ml
+
First dose vaccine within 12 hrs.

percutaneous exposure



Sexual Contact - Ig within 14 days.

Adult 3 doses 0, 1, 2

>20 yrs - 1ml = 20 µg im deltoid

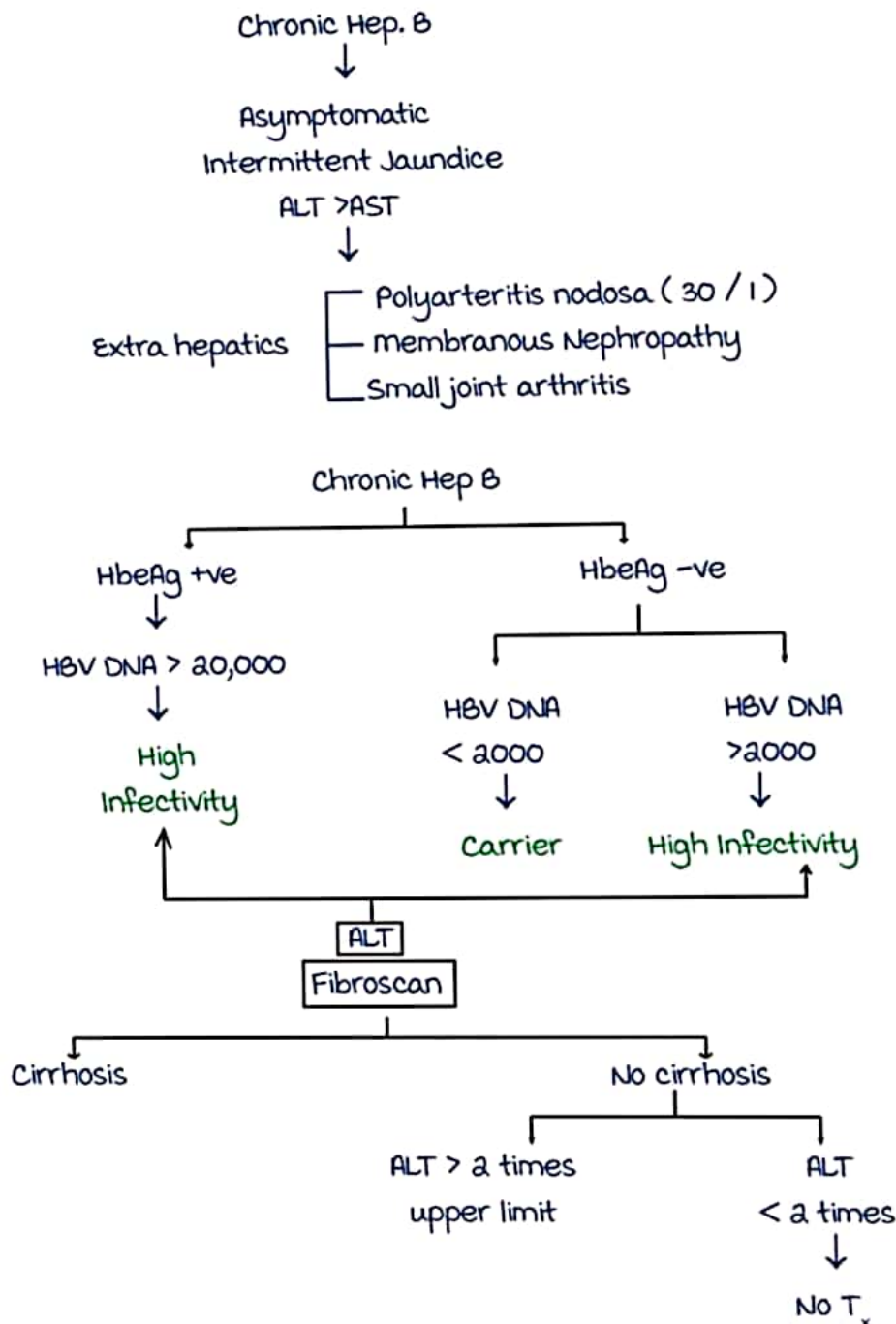
<20 yrs 0.5 - ml = 10 µg im deltoid

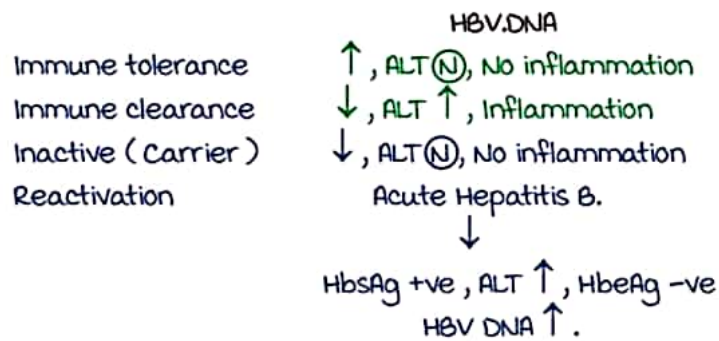
CKD pt - 4 doses (0, 1, 2, 6)
(2ml)

≤ 20 yrs CKD pt. - 4 doses (0, 1, 2, 6)
(0.5-ml)

Chronic Hepatitis

00:47:58





Chronic Hepatitis B Epidemiology

01:00:12

- Age of acquirement of virus : Perinatal → Chronic
- Grade of liver disease
 - ⊕ Determines risk of progression
 - Degree of replication .
- Replicative Phase HBV DNA > 20,000 .
- Spontaneous seroconversion 1 - 1.5 %
- Intrahepatocyte HbcAg is present

Clinical Features

01:02:23

1. Fatigue
2. Intermittent jaundice
3. Acute exacerbations
4. Complications of cirrhosis
5. Extrahepatic
 - PAN
 - Arthritis
 - membranous Nephropathy
5. Bilirubin 3 - 10 mg /dl .

Treatment

1. Peg interferon

s/c	30 %	
HbsAg	→	HbsAg -ve
+ve		

No effect seen in :-

1. Young asians
2. HbeAg -ve
3. Cirrhosis

Side effects:-

Thyroiditis
Psychosis
Bone marrow suppression

2. Lamivudine (YMDD mutation)

±

Adefovir (nephrotoxic)

3. DOC - Entecavir / Tenofovir

(0.5 mg daily) (300 mg daily)



Tenofovir alafenamide

Advantages

1. ↓ Systemic toxicity / nephro / bone
2. Dose . 25 mg (low dose)
3. more stable

HbsAg +ve → HbsAg -ve only drug interferon α
20%-30%

HPE - Ground glassing of hepatocyte .

Hepatitis D

01:12:27

• RNA delta virus .

Super infection { Chronic HBV HbsAg , anti Hb C IgG
Acute HDV anti HDV IgM +ve
↑ Cirrhosis (anti LKM III antibody)

Coinfection : Acute hepatitis B anti Hbc IgM +ve
(B + D) 2nd peak of jaundice anti HDV IgM +ve



- No risk for cirrhosis .
- Risk for fulminant hepatitis (20 %)

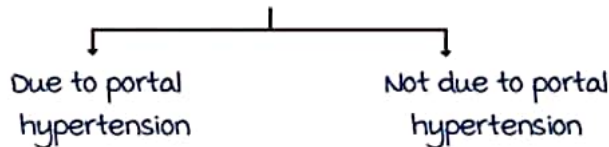
ASCITES

Decompensation in cirrhosis : Portal hypertension +

Introduction to Ascites

00:00:42

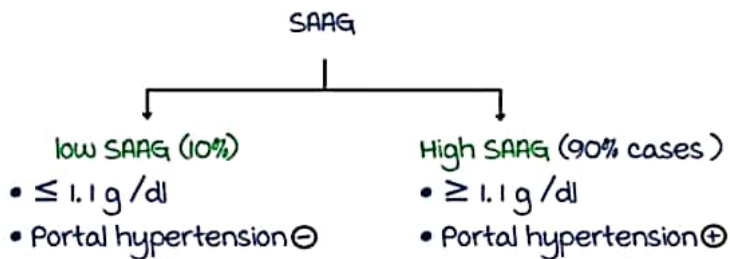
- Definition : Fluid in peritoneal cavity
- Ascites is the **earliest complication** of portal hypertension.
Note - Portal hypertension and splenomegaly appears together
- Cause :



Serum Ascitic Fluid Albumin Gradient (SAAG)

00:02:17

SAAG = Serum albumin - Ascitic fluid albumin



Low SAAG ascites

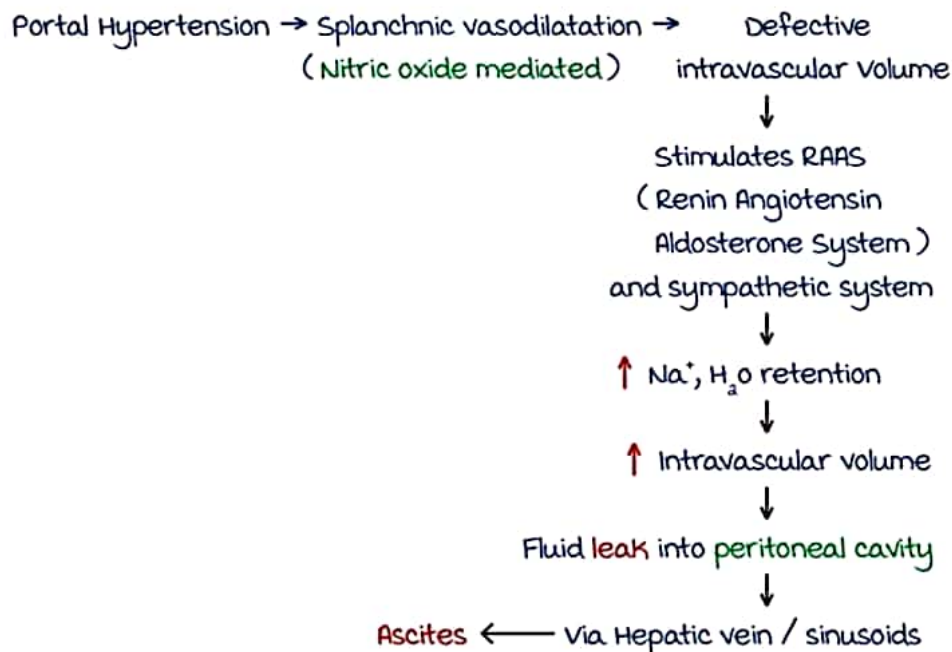
- High ascitic fluid albumin
Peritoneal carcinomatosis > Peritoneal TB > Peritonitis
- Low serum albumin
Nephrotic syndrome

High SAAG ascites

- Low protein ascites (No albumin leak via sinusoids)
 - Sinusoidal pathology
 - Proteins in ascitic fluid ↓ ↓Cause : cirrhosis with portal hypertension
- High protein ascites
 - Hepatic vein pathology
 - Proteins in ascitic fluid ↑ ↑Cause : Budd chiari syndrome, constrictive pericarditis

Pathophysiology of ascites in portal hypertension

00:07:01



Note :

- First sign of decompensation : Splenomegaly > Portal hypertension
- First complication of decompensation (portal hypertension) : Ascites
- Ascites in portal hypertension without decompensation : Alcoholic hepatitis

Diagnosis of ascites

00:13:46

- Ultrasound - minimum 100 ml of ascitic fluid can be detected
- Shifting dullness - 500 ml
- Fluid thrill - 1000 ml
- Neck veins +ve - Constrictive pericarditis

Ideal site for Ascitic fluid tap

Left lower quadrant 3 cm cephalad and 2 cm medial to anterior superior iliac spine

Assessment of ascitic fluid

00:15:26

Normal Ascitic fluid :

WBC < 500 cells / μ l

PMN (poly morpho nuclear leucocytes) < 250 cells / μ l

Hemorrhagic Ascites :

RBC > 10,000 cells / μ l $\Rightarrow$ Pink ascitic fluid
 milky Ascitic fluid

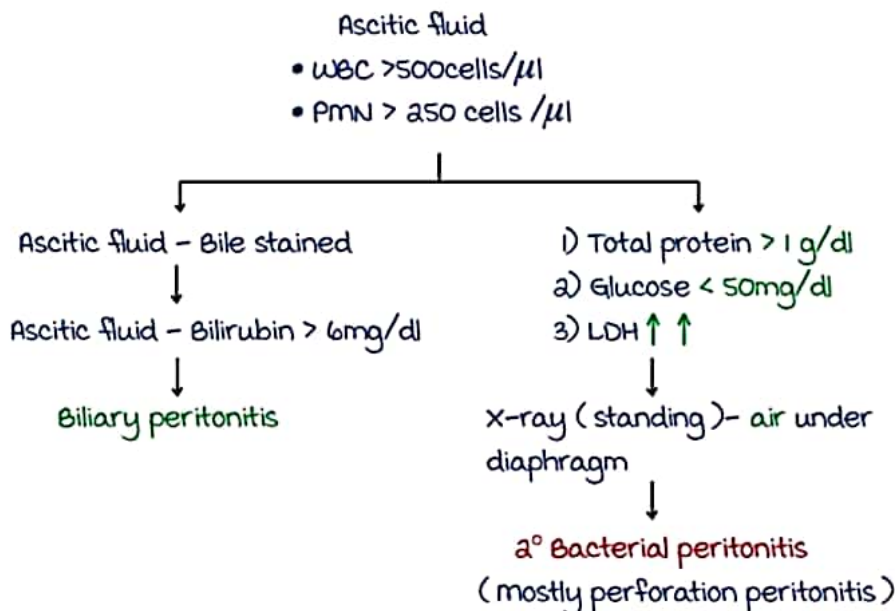
Chylous

Pseudochylous

	Chylous	Pseudochylous
• Onset	sudden	Gradual
• Cause	Acute obstruction/trauma to lymphatic duct	Neutrophils in ascitic fluid due to inflammation
• microscopic examination	lymphocytosis	mixed cellular reaction, cholesterol esters, neutrophils
• Triglycerides	> 110mg/dl	< 50 mg/dl
• Lipoprotein electrophoresis	chylomicrons present	chylomicrons absent

Approach to a case of ascites

00:19:03



SBP, MNB, CNNA

00:23:17

Spontaneous Bacterial Peritonitis (SBP)

- Ascitic fluid - culture positive
- PMN : > 250 cells / μ l
- No evidence of intra-abdominal, surgically treatable source of infection
- most common organism : E-Coli

monomicrobial Non-neutrocytic Bacterascites (MNB)

- Culture positive
- PMN < 250 cells/ μ l
- Most common cause - Gram positive organism

Culture Negative Neutrocytic Ascites

- Culture negative
- PMN > 250 cells/ μ l
- Good immunity

management

- SBP : Inj Cefotaxim 2g IV TDS x5 days
- Risk of recurrence is high
- Prophylaxis
- Prior SBP or Cirrhosis + Portal HTN: Norfloxacin 400mg OD
- Active GI bleed : Inj Ceftriaxone 1g IV x7days

Management of Subacute Bacterial Peritonitis

00:28:18

- Salt restriction

monitor urine sodium.

Urine $\text{Na}^+ : \text{K}^+$ ratio $> 1 \Rightarrow$ require further salt restriction

$< 1 \Rightarrow$ start drug therapy

- Diuretics

Spironolactone 100 mg + Furosemide 40 mg

↓ Not responding

Add midodrine

↓ Not responding

Therapeutic paracentesis every 2 weeks

↓ Not responding

TIPPS

(Transjugular intrahepatic portosystemic shunt)

Refractory Ascites

Diuretic intolerant
ascites

Resistant ascites

[not responding to Spironolactone 400mg
+
Furosemide 160mg
+
Salt restriction]

HEPATIC ENCEPHALOPATHY

Definition

00:00:07

Hepatic Encephalopathy (HE) or Portosystemic encephalopathy (PSE) is a **reversible syndrome** of impaired brain function, occurring in patients with **advanced liver failure**.

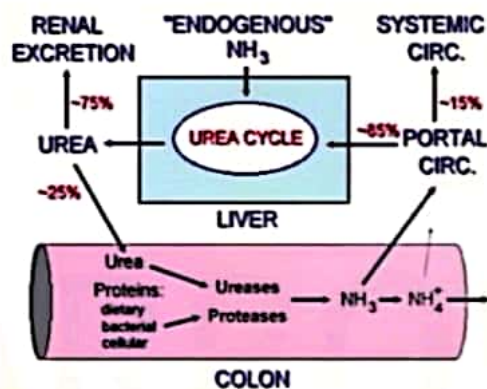
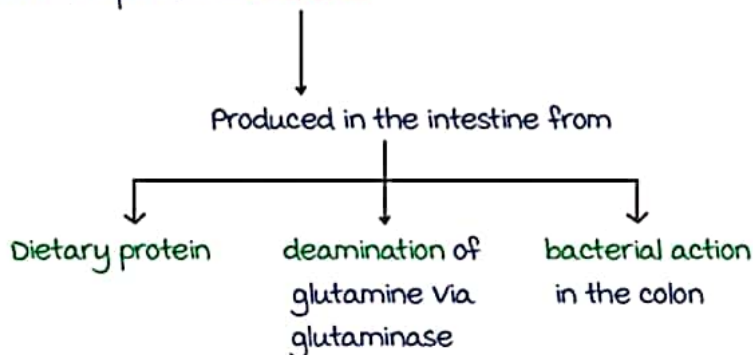
Hepatic encephalopathy

- **Complication** of portal hypertension (PHTN)
- A/K/A **portosystemic encephalopathy**
- **Reversible**
- Precipitating factor present
- Predominant cell affected - **Astrocyte** (Alzheimer's type II astrocyte)
- Grading system - **West Haven**
- Major toxin involved - **Ammonia**

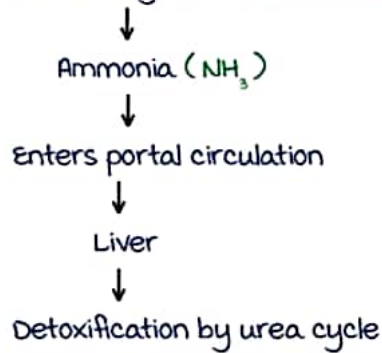
Gut - derived neurotoxins

00:02:55

- most important - **Ammonia**



- Ammonia is absorbed by **non - ionic diffusion**



- In hepatic encephalopathy

Liver dysfunction - No urea cycle

↑ Ammonia in circulation

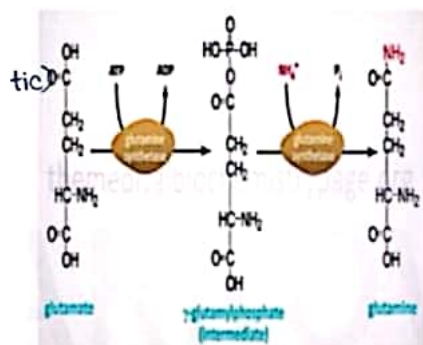
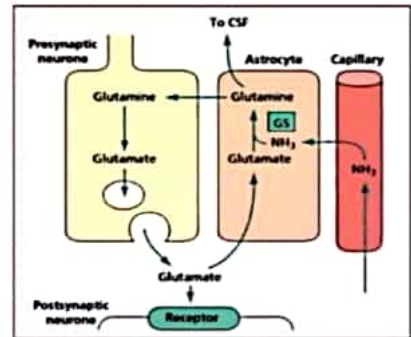
Enters brain - Astrocyte

In Astrocyte - Glutamate + NH_3

↓ Glutamine synthetase

Glutamine

Enters neuron → Converted to Glutamate



Acts on **NMDA Receptor** (Post synap-

Neurotoxicity

- Extra cellular and cerebrospinal fluid(CSF) glutamate - ↑↑
- Total brain glutamate - ↓↓

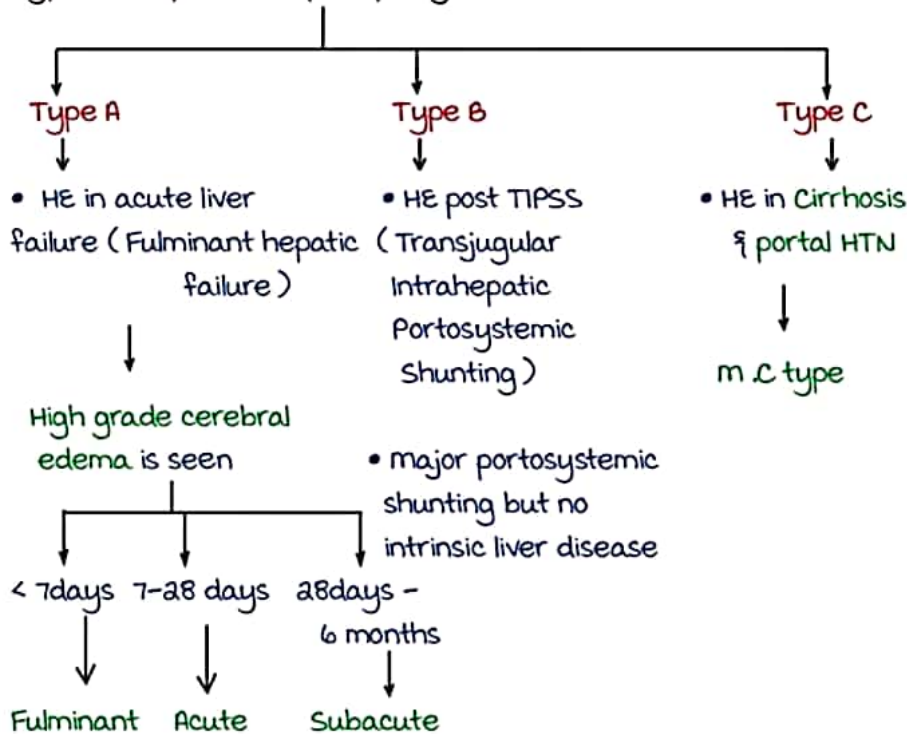
Endotoxins and types of hepatic encephalopathy

00:07:11

Other endotoxins Causing HE

- 1) mercaptans (degradation of methionine in the gut)
- 2) Phenols
- 3) Free fatty acid
- 4) Gamma Amino Butyric Acid (GABA)
- 5) Octapamine
- 6) Aromatic Amino acids
- 7) manganese

Types of Hepatic encephalopathy



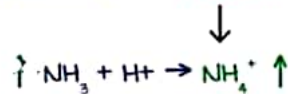
Precipitating factors

00:09:33

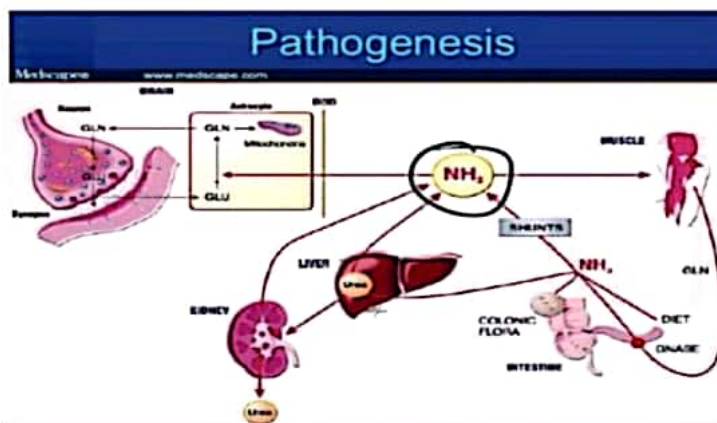
- 1) ↑ nitrogen load - due to - constipation
GI bleeding
Dietary protein
Azotemia (uremia)

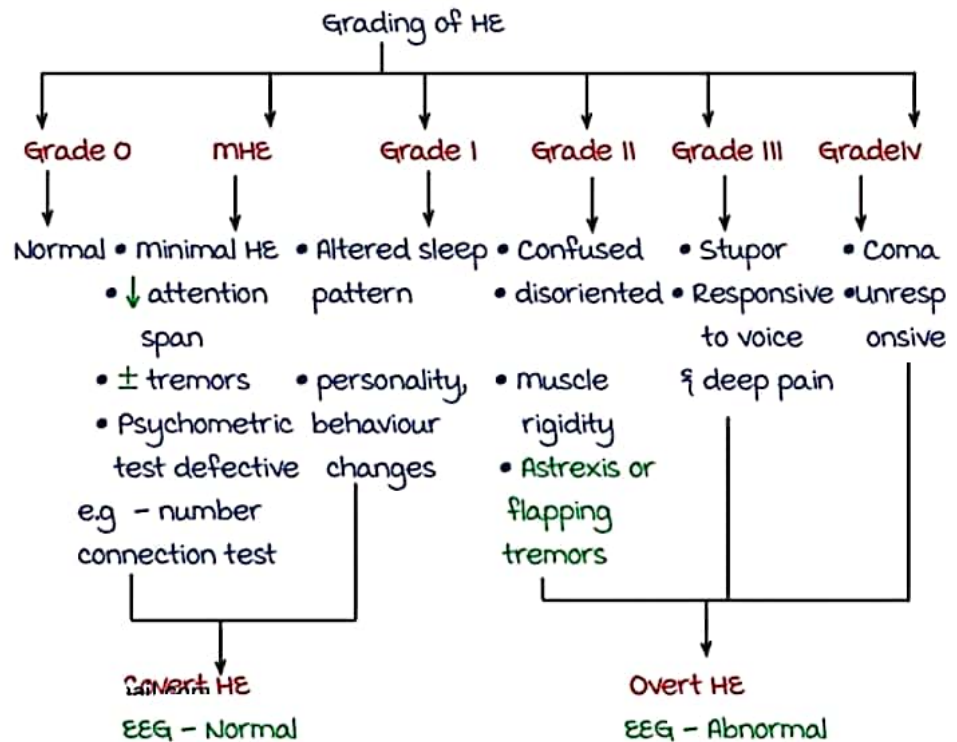
2) Infection - sepsis

- In vomiting → Hypovolemia, hyponatremia → Alkalosis



- CNS drugs
- Dehydration





Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Hepatic encephalopathy investigation and treatment

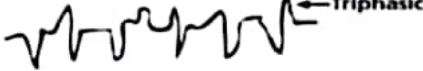
00:17:42

Electroencephalography (EEG)



Triphasic waves - HE - Grade IV

Stages of EEG and Clinical state

Stage of EEG	Clinical State
	Alert
	Drowsy
	Stuporose
	Coma
	Deep coma
	Terminal

Treatment

- 1) Lactulose containing bowel wash
non - absorbable disaccharide (metabolized by intestinal bacteria)
reduce pH $\rightarrow \text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+$
- 2) Rifamixin $\rightarrow$ 400mg TDS / 550mg BD
- 3) Acarbose
- 4) L - ornithine , L- aspartate
- 5) Sodium benzoate

HEPATORENAL SYNDROME

Hepatorenal Syndrome

00:00:21

- 1) Diagnosis of **exclusion**
 - 2) Structurally **normal** kidney
- ↓
- But functionally **abnormal** kidney → due to portal hypertension (PHTN)

↓

Splanchnic vasodilation

↓

Activates renin angiotensin system (RAS)

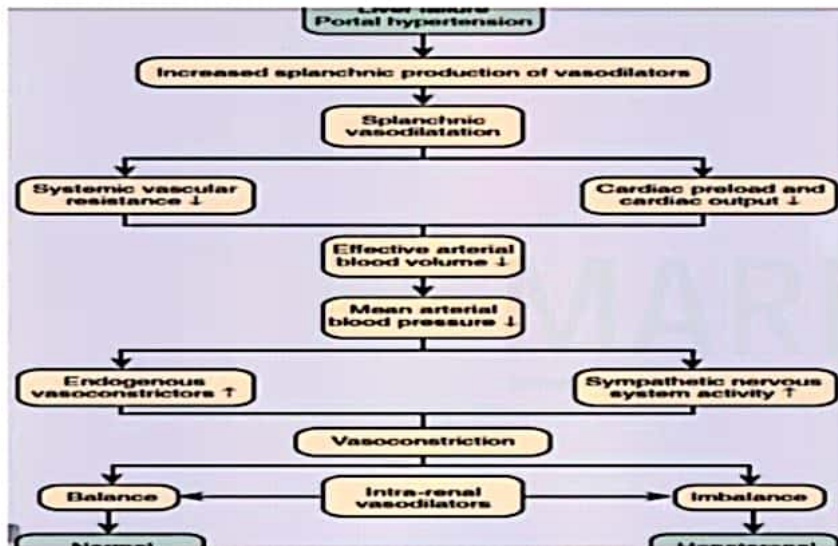
↓

Severe intra renal vasoconstriction

- 3) In ultrasound - Normal kidney, urine analysis - Normal
- 4) **Prerenal** impairment - excluding - GI loss

Diuretics use

↓ Albumin



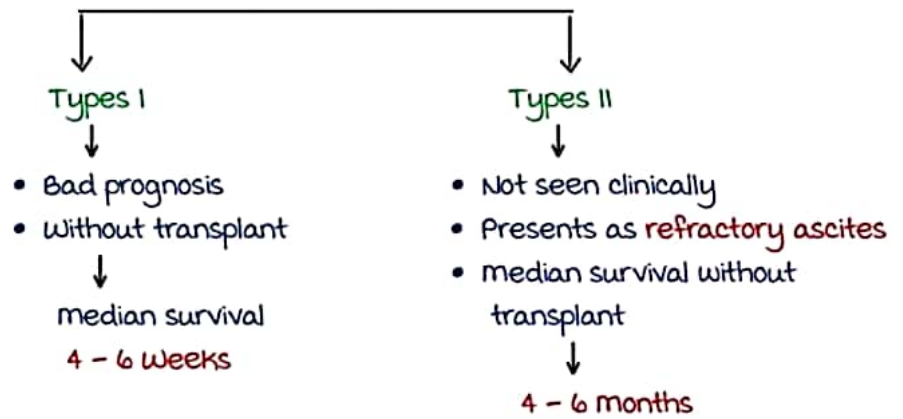
Criteria, Types, Treatment of Hepatorenal system

00:06:55

Criteria

- 1) Cirrhosis + PHTN
- 2) Acute renal failure (acute kidney injury)
- 3) No structural kidney disease
- 4) urinalysis - Normal
- 5) No GI loss / no Hypoalbuminemia
- 6) No diuretic overdose

Types of HRS



Treatment

- Definitive treatment - Liver transplant
- Vasoconstrictors - for splanchnic vasoconstriction (Only in patients awaiting transplantation)

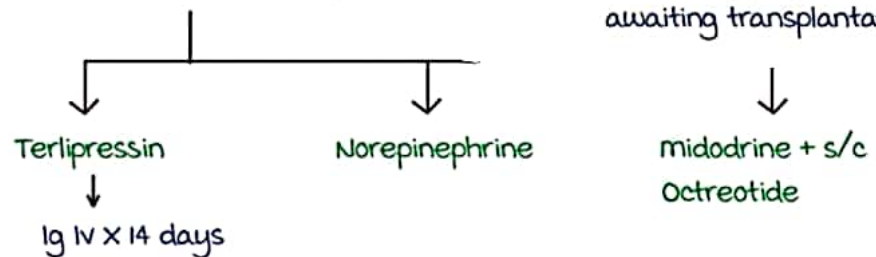


Table 2. Vasoconstrictor Drugs for the Treatment of Hepatorenal Syndrome

Drug	Mechanism of Action	Dose	Comments
Terlipressin	Vasopressin analogue	1 mg IV every 4-6 h; increase to 2 mg every 4-6 h if there is no improvement in Scr (decrease by 25% by day 3) up to a maximum of 12 mg/d as long as there are no side effects; maximal treatment 14 d	Not available in the United States
Norepinephrine	α -Adrenergic agonist	0.5-3.0 mg/h (continuous infusion); titrate to achieve a 10-mm Hg increase in MAP	Requires ICU; in countries where terlipressin is not available, norepinephrine can be used as a initial therapy in ICU patients or as an alternative in patients in whom midodrine + octreotide has failed
Midodrine + octreotide	α -Adrenergic agonist (midodrine); somatostatin analogue (octreotide)	Midodrine: 7.5-12.5 mg orally 3 $\times$ /d; titrate to achieve a 10-mm Hg increase in MAP from baseline; octreotide: 100-200 μ g SC 3 $\times$ /d	

Note: All vasoconstrictors should be given in combination with 25% IV albumin.

Abbreviations: ICU, intensive care unit; IV, intravenous; MAP, mean arterial pressure; SC, subcutaneous; Scr, serum creatinine

Am J Kidney Dis. 2016;67(2):318-328

Pseudohepatorenal Syndrome

- Liver failure + Renal failure

Eg - In leptospirosis (Weil's disease)

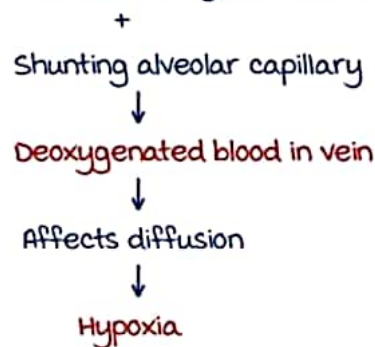
Hepato pulmonary Syndrome

00:10:46

- Clinical triad of
 - Liver disease (usually portal hypertension with or without cirrhosis)
 - Hypoxemia
 - Intra pulmonary vascular vasodilation

Pathogenesis

- Due to nitric Oxide (No) → Intrapulmonary vasodilation



- $\uparrow (A - a) O_2$ - (A - alveolar, a - artery)
- C/F - Platypnea (Dyspnea on lying down)
Orthodeoxia (Shunting of deoxygenated blood $\uparrow$ on standing)
- Vascular abnormalities predominate in lower lung fields
- Absence of Cardiopulmonary diseases
- I.O.C - Bubble Echocardiography
- Treatment - Liver transplant

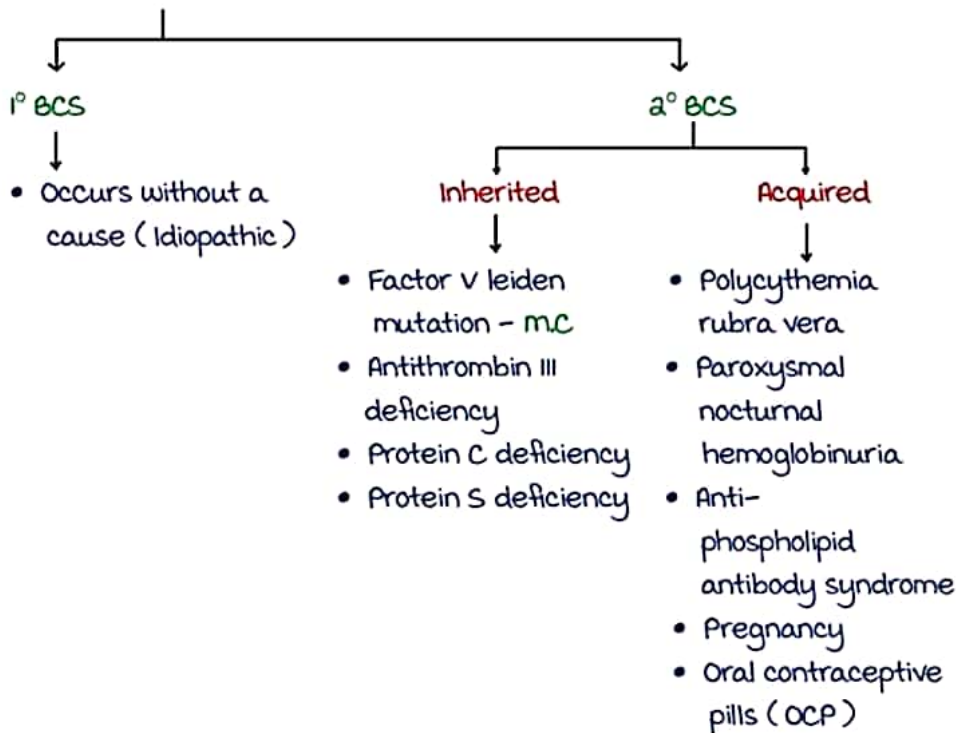
VASCULAR DISORDERS OF LIVER

Budd Chiari Syndrome (BCS)

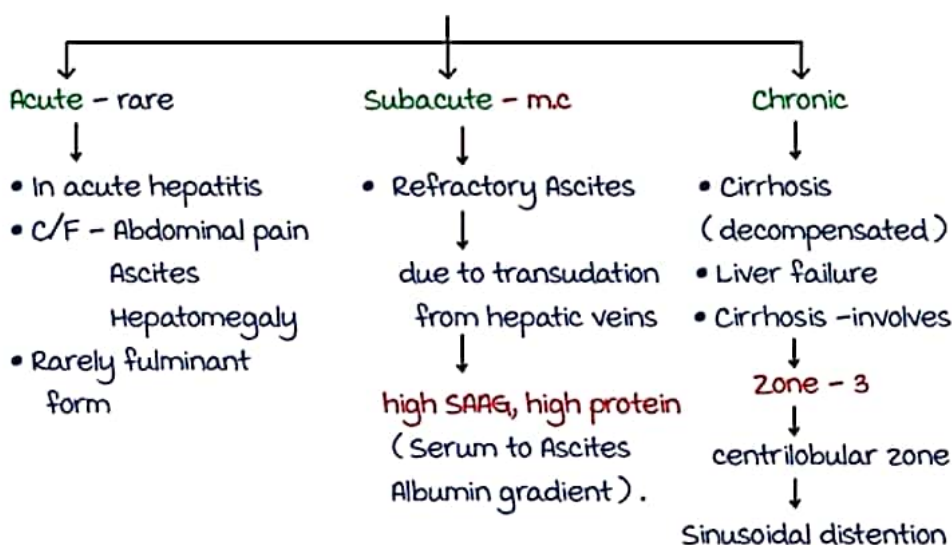
00:00:14

- Obstruction at any site from the **efferent vein** of the acinus to the **entry of IVC** (inferior vena cava) into right atrium
 - **m.c site** - hepatic vein or terminal IVC
 - Females : 35 - 40 yrs
 - Post partum period
- } → m.c

Classification

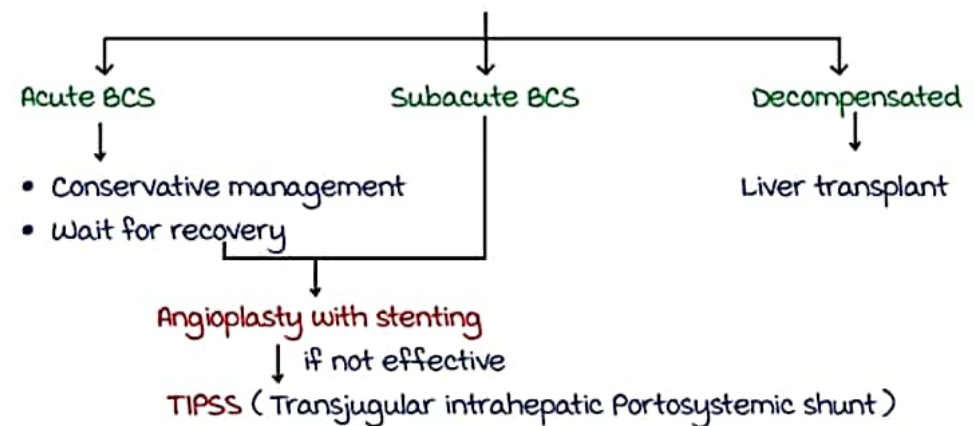


Types of clinical presentation :



- Screening test - ultrasound with hepatic venous doppler
 - ↓
- I.O.C - CECT
 - Caudate lobe hypertrophy - shows hyperintensity
 - Occlusion of hepatic vein
- For nodules/ hemorrhage in the liver - MRI
- Gold standard test - Venography

Treatment



- Poor prognosis - 90% die within 3yrs

Extra hepatic portal venous obstruction

00:10:34

- 1st order portal vein obstruction
 - ↓
 - due to umbilical sepsis > thrombosis
- Seen in children (3-8 yrs)
- C/F: massive upper GI bleeding
 - +
 - massive splenomegaly
- No ascites / no hepatomegaly
- No cirrhosis
- Normal liver function test (LFT)
- Good prognosis.

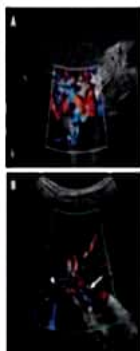
- management - manage upper GI bleed

↓
Endoscopic variceal ligation

- Complications - **Growth retardation**
Portal biliopathy - due to **cavernoma** formation
(collaterals - compress biliary system)
- Screening test - ultrasound and colour doppler - shows cavernoma formation
- **I.O.C** - CECT - shows **leash like cavernous appearance**

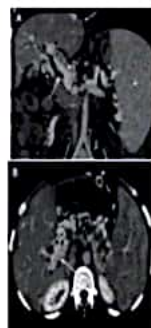
GROWTH RETARDATION

- Deprivation of portal blood flow leading to reduction of hepatotropic Factors needed for normal growth.
- Malabsorption secondary to portal hypertensive enteropathy.
- Early satiety due to massive splenomegaly
- Growth hormone (GH) resistance evidenced by high levels of GH and low levels of Insulin-like growth factor-1 (IGF-1)
- Anemia and Hypersplenism



USG AND COLOUR DOPPLER

- 94-100% sensitive and 96% specific in the diagnosis of EHVPO.
- Non visualization of portal vein with multiple tortuous anechoic structures at porta representing **Cavernoma** formation.
- Liver size and echotexture is normal.



CECT ABDOMEN

- The exact extent of portal vein thrombosis with or without extension to intrahepatic divisions, splenic and superior mesenteric vein can be visualized.
- The multiple portoportal and portosystemic collaterals and thin gallbladder varices not clearly seen on USG are better depicted on CT.
- CBD and IHBR dilatation seen
- The main role of CT lies in ruling out other causes

- If **Refractory** or failed endoscopy } Surgical management
↓
mesenterico - Left portal vein bypass

SURGERY



INDICATIONS FOR SURGERY

- Persistent Variceal bleeding who fail endoscopic therapy
- Presence of gastric or ectopic varices not amenable to endoscopic management
- Symptomatic Portal Biliopathy
- Growth failure
- Symptomatic hypersplenism

MESENTERICO-LEFT PORTAL VEIN (REX) BYPASS

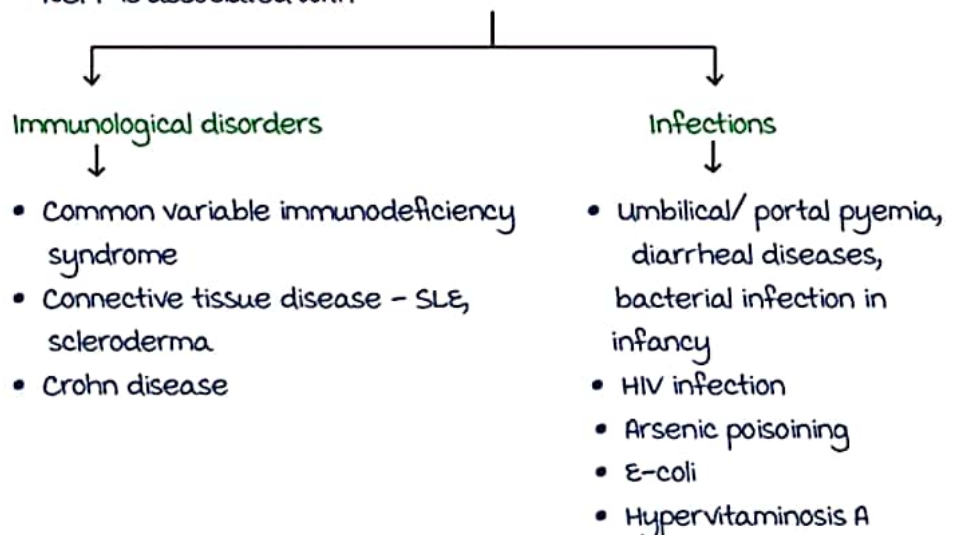
- Most physiological and the shunt of choice as it restores the hepatic blood flow.
- Besides correcting portal hypertension, it also abolishes the systemic manifestations of EHPVO

- Idiopathic portal hypertension
- Seen in adolescents & young adults
- A/K/A Obliterative portal venopathy
hepatoportal sclerosis
- 2nd or 3rd order portal vein occlusion
- C/F - massive upper GI bleed
massive splenomegaly
No hepatomegaly / ascites
- LFT - Normal, absence of serum markers - hepatitis B, C
- Good prognosis
- Negligible chances for cirrhosis
- Diagnosis - 1st line : doppler ultrasound - thickened portal vein
2nd line : biopsy - Shows sclerotic portal vein with
Normal hepatic vein, no cirrhosis



Thickened portal vein

- NCPF is associated with



Post sinusoidal obstruction syndrome

00:23:18

- Obstruction before the efferent vein
- Seen post bone marrow transplant



due to heavy conditioning with cyclophosphamide, Busulfan
Before transplantation

PORTAL HYPERTENSION

- **Decompensated cirrhosis** → present only in case of portal hypertension
- Portal hypertension : responsible for all complications of cirrhosis of liver :
 - GI bleed
 - Ascites → SBP (spontaneous bacterial peritonitis)
 - HE (Hepatic Encephalopathy)
 - HRS (Hepatorenal syndrome)
 - HPS (Hepatopulmonary syndrome)

Definition and causes of portal hypertension

00:00:54

Definition :

- Hepatic sinusoidal pressure > 6 mm Hg
- Portal venous pressure > 12 mm Hg

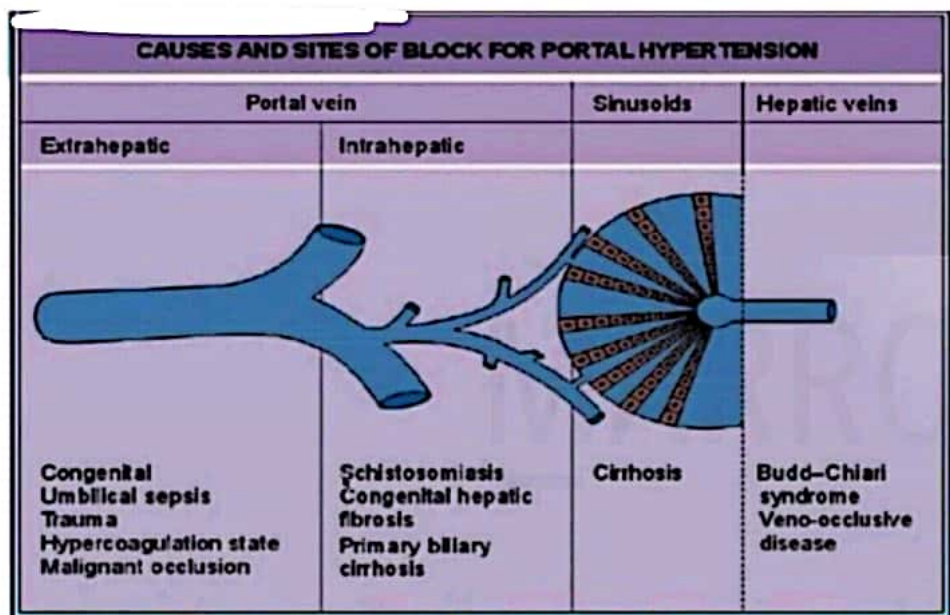
Causes :

- Prehepatic
 - **1st order portal vein** → EHPVO (Extra hepatic portal vein occlusion)



No cirrhosis

- Splenomegaly
- upper GI bleeding
- Posthepatic
 - Efferent vein → hepatic vein → IVC
 - Budd Chiari syndrome → cirrhosis
 - Chronic constrictive pericarditis
 - Tricuspid regurgitation
 - Right heart failure
- Intrahepatic
 - divided into :
 - Presinusoidal : NCPF (Non cirrhotic portal fibrosis)
 - Schistosomiasis
 - Sarcoidosis
 - Primary Biliary cirrhosis
 - Sinusoidal
 - Postsinusoidal : After bone marrow transplant



Portal hypertension in cirrhosis

00:06:29

- $\text{Portal pressure} = \text{Flow (F)} \times \text{Resistance (R)}$

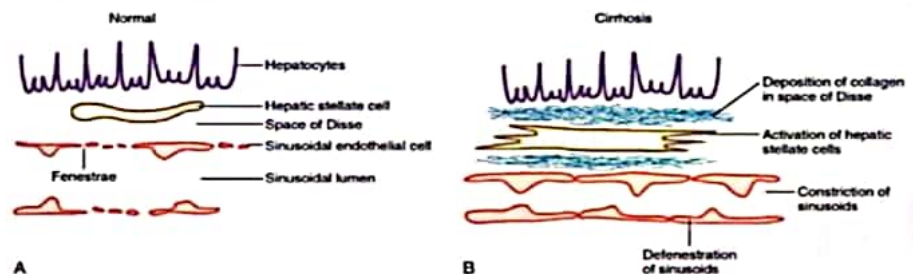


FIGURE 92-2. Anatomy of the hepatic microvasculature. **A.** Normal sinusoidal microanatomy is depicted. The sinusoidal lumen is lined by fenestrated sinusoidal endothelial cells that allow the transport of macromolecules to the abluminal space of Disse. Quiescent hepatic stellate cells reside within this space, adjacent to hepatocytes and endothelial cells. **B.** In cirrhosis, a number of changes occur in the hepatic microcirculation, including loss of fenestrae in endothelial cells (defenestration), constriction of sinusoids, and activation of hepatic stellate cells with ensuing deposition of collagen and increased contractility.

- Portal hypertension in cirrhosis is due to :
 1. Nodules compressing sinusoid or $\uparrow$ resistance
 2. Defenestration and constriction of sinusoids
- Portal hypertension is manifested by :
 - Caput medusae



Mechanism/s

Portal hypertension causes backflow from the portal vein to the para-umbilical veins. The increased pressure and blood volume distend the veins.

- Clinically :
 1. Thrombocytopenia due to hypersplenism
 2. Splenomegaly
 3. Upper GI endoscopy → to look for varices
- most important complication → ascites

Portal cirrhosis – portal vein

- 7.5 cm long and runs dorsal to hepatic artery and bile duct
- At hilum,
 - Umbilical vein drains to Left portal vein
 - Cystic vein drains to Right portal vein
- High compliance, Low resistance (hepatic arterial buffer response)
- In case of portal vein occlusion → Hepatic artery.

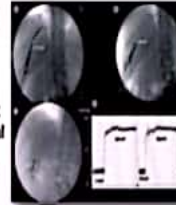
Hepatic venous pressure gradient (HVPG)

00:10:20

= Wedged hepatic venous pressure (WHVP) – free Hepatic venous pressure (FHVP)

Is the difference between the wedged (WHVP) and the free hepatic venous pressures (FHVP).

HVPG represents the gradient between pressures in the portal vein and the intra-abdominal portion of inferior vena cava.



- 1 – 5 mm Hg : normal
- > 10 mm Hg : clinically significant portal hypertension
- > 12 mm Hg : High risk for bleeding
- WHVP is almost equal to sinusoidal pressure
- Use of Hepatic venous pressure gradient (HVPG) in the differential diagnosis of portal hypertension :

Type of portal Hypertension

Prehepatic

WHVP

FHVP

HVPG

N

N

N

Hepatic — Presinusoidal
 Sinusoidal
 Postsinusoidal

N

N

N

↑

N

↑

↑

N

↑

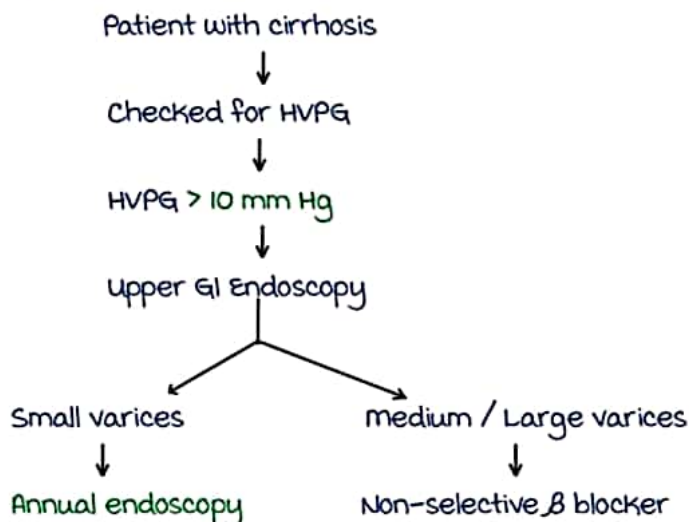
Posthepatic

↑

↑

N

- Risk of bleeding $\propto$ HVPG
- Implication :



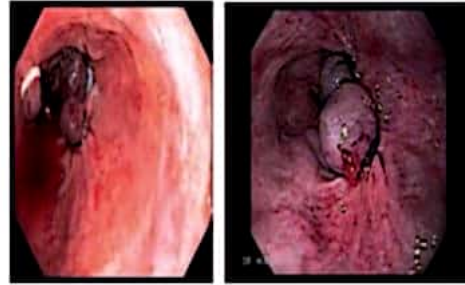
(Propranolol or Carvedilol)

↓ intolerant

Or

↓ still ↑ HVPG

Endoscopic variceal ligation



Drug for treatment of portal hypertension

00:16:42

- Portal pressure = Flow X Resistance
- Drugs that ↓ portal blood flow :
 - Non-selective β -Adrenergic blocking agents } prophylaxis
 - Somatostatin and its analogues } Acute upper GI Hemorrhage
 - Vasopressin
- Drugs that ↓ intrahepatic Resistance :
 - α_1 -Adrenergic blocking Agents Eg : Prazosin
 - Angiotensin receptor blocking agents
 - Nitrates } no therapeutic role

Esophageal variceal hemorrhage

00:17:44

- Primary prophylaxis for esophageal variceal hemorrhage →
- Non-indicated therapies :
 - variceal sclerotherapy : Not effective
 - Surgical shunt : ↑ mortality
 - TIPSS (Transjugular Intrahepatic portosystemic shunt) : lack of evidence
 - Cyanoacrylate injection in gastric varices : effective ,
↑ complication risk

- Vasoactive agents used in management of acute variceal hemorrhage :

Octreotide (SMT analogue)	Initial IV bolus of 50 micrograms (can be repeated in first hour if ongoing bleeding)	2-5 days
Vasopressin	Continuous IV infusion of 50 µg/hr Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min It should always be accompanied by IV nitroglycerin at a starting dose of 40 µg/min, which can be increased to a maximum of 400 µg/min, adjusted to maintain a systolic blood pressure 90 mm Hg.	24 hours
Drug	Recommended Dose	Duration
Terlipressin (VP analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding Maintenance: 1 mg IV every 4 hours to prevent rebleeding	2-5 days

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

- management of acute esophageal varices :

Vasoactive Drugs : Terlipressin

or

Octreotide

or

Vasopressin



Blood transfusion (7-9 g/dl)



IV Antibiotic (ceftriaxone 1g/24 hours)



EGD (Esophagogastroduodenoscopy) : done within 12 hours of admission + patient →

Hemodynamically stable



Variceal source confirmed

Endoscopic variceal Ligation



risk of re-bleeding ↑

TIPS

modified Child -Pugh scoring

TABLE 92-4 Child-Turcotte-Pugh Scoring System and Child-Pugh Classification

Parameter	Numerical Score		
	1	2	3
Ascites	None	Slight	Moderate/severe
Encephalopathy	None	Slight/moderate	Moderate/severe
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds increased)	1-3	4-6	>6
Total Numerical Score		Child-Pugh Class	
5-6		A	
7-9		B	
10-15		C	

- **Nutritional status** : was used in the conventional scoring system

Rockall risk score

- Predicts **poor prognosis**
(Rebleeding and mortality → upper GI hemorrhage)
- Uses **clinical criteria** (↑ age , comorbidity , shock)
+
Endoscopy findings

Forrest classification

- Endoscopic
- Assesses risk for :
→ Re-bleeding
→ Surgical requirement
→ mortality
- Classified as : Active bleed , Recent bleed , Lesion without bleeding

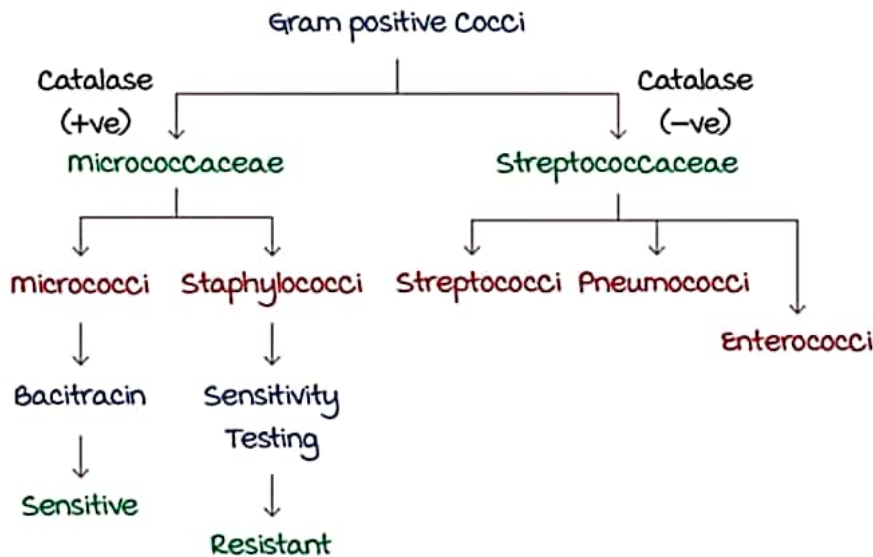
Forrest classification system with predictive prognosis

Forrest Classification	Rebleeding Incidence	Surgical Requirement	Incidence of Death
Type I: Active Bleed	55-100%	35%	11%
Ia: Spurting Bleed			
Ib: Oozing Bleed			
Type II: Recent Bleed	40-50%	34%	11%
Ila: Non-Bleeding Visible Vessel (NBVV)	20-30%	10%	7%
Ilb: Adherent Clot			
Type III: Lesion without Bleeding	10%	6%	3%
Flat Spot	5%	0.5%	2%
Clean Base			

INFECTIOUS DISEASE-1

Staphylococci

00:02:15



- Staphylococcus in nutrient agar → Golden yellow pigmented colonies (β -carotene)
- Blood agar → mild positive for hemolysis
- Specific medium → Ludlam's medium
- Staph aureus v/s CONS:
 - 1) Coagulase test +ve
 - 2) Thermonuclease +ve
 - 3) DNase / phosphatase +ve
 - 4) mannitol fermentation $\oplus$
 - 5) Potassium tellurite agar → Black colonies
- most common method of typing → Phage typing (mc type -80/81)
- Resistance → β -lactamase (Phage / Plasmid mediated)
MRSA (Chromosomally / Genitically mediated- mec A gene)
- MRSA is identified by Disk diffusion method by using Oxacillin / Cefoxitin
- mc site of colonization of staph. aureus → Anterior nares

Virulence factors :

00:13:06

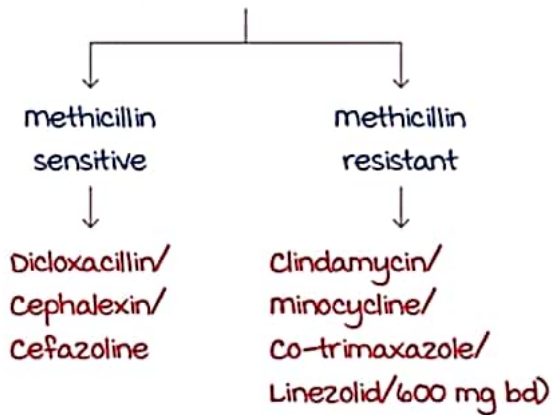
- I. Cell wall-based Protein A - Antiphagocytic, chemotactic,
Co-agglutination
- II. Leucocidin (Panton valentine toxin) + γ hemolytic toxin $\rightarrow$
Synergohymenotropism $\rightarrow$ Destroys macrophages
- III. Enterotoxin - Preformed toxin
Incubation period - 6 hrs
Heat stable
Acts on vagus & vomiting centre
No fever
No role for antibiotics
- IV. Toxic shock syndrome Toxin / Pyrogenic exotoxin C /
Enterotoxin F
 - Superantigen
 - a/w vaginal tampons
 - MC seen in actively menstruating females
 - Presents with fever with hypotension
 - MODS
 - Rx: Clindamycin
- V. Exfoliative toxin
 - Staphylococcal scalded skin syndrome (SSSS)
 - Nikolsky sign (+ve)

Clinical symptoms :

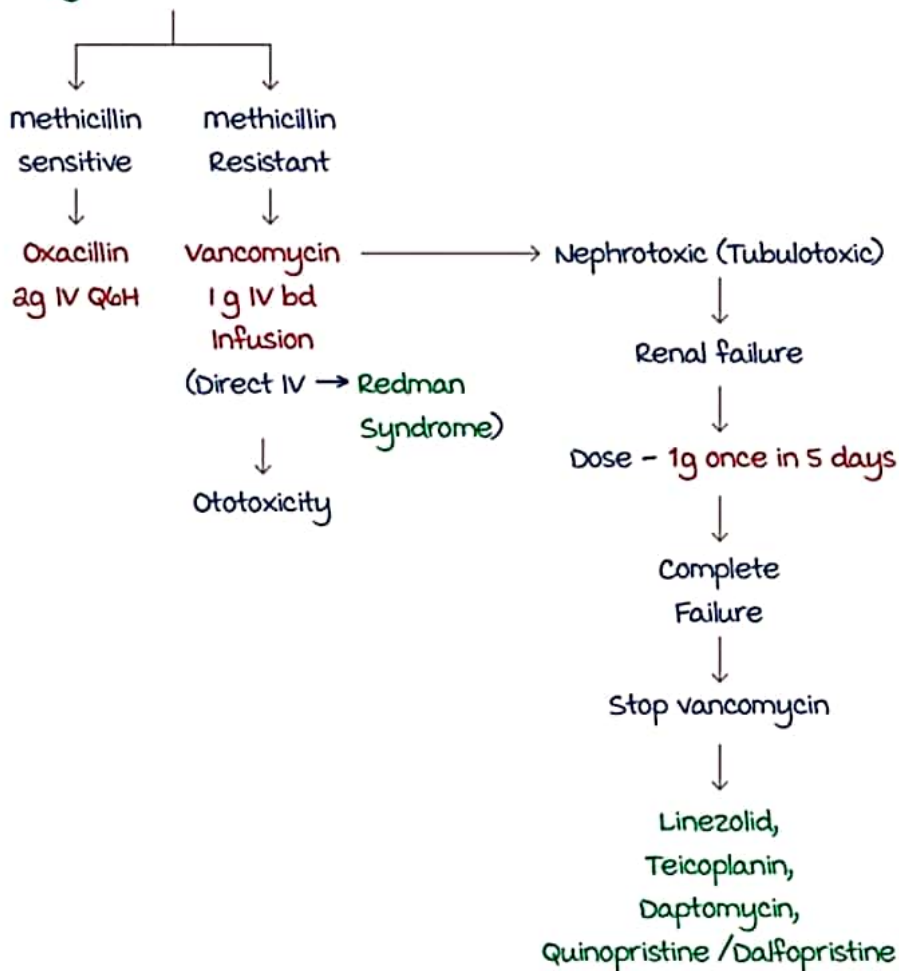
- 1) Skin and soft tissue infections
- 2) Breast abscess / mastitis
- 3) Folliculitis / furuncle / Carbuncle
- 4) Septic arthritis / Osteomyelitis
- 5) Pneumonia
- 6) Endocarditis
- 7) Tropical pyomyositis

Treatment :

I skin & soft tissue infections



II. Systemic infections



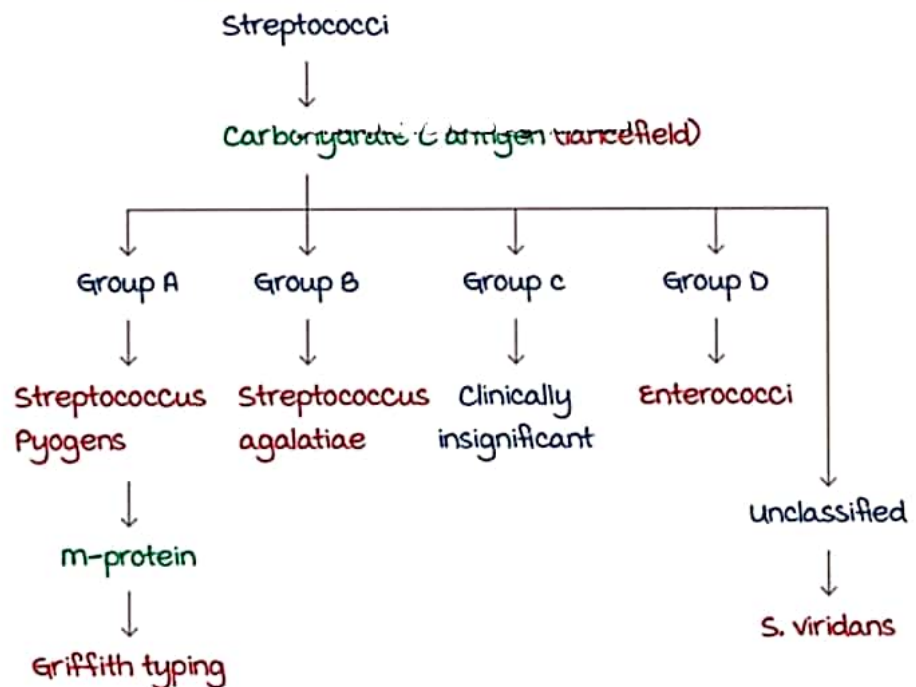
III. VRSA → Telavancin

- mc → *Staphylococcus epidermidis*
- most abundant species on skin
- Early prosthetic valve endocarditis
- mc infection associated with implantable foreign bodies
- *Staphylococcus saprophyticus* → Complicated UTI in pregnancy

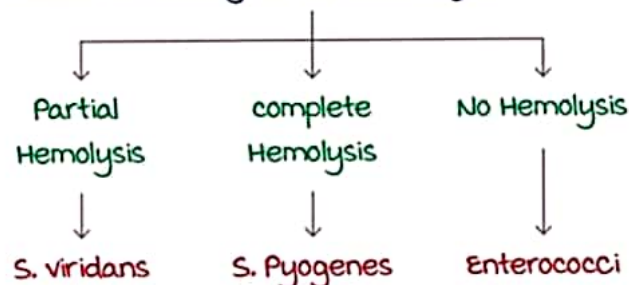
Streptococcus:

00:35:04

- Catalase negative



- Based on Hemolysis, (5% Blood agar)



- catalase test → Staph v/s strep
- Bile solubility & Inulin fermentation → Strep v/s Pneumococci
- PYR test & failure to ferment ribose → Strep. pyogenes
- CAMP test & Hippurate hydrolysis → Strep. agalactiae

Antigenic structure :

- Cell wall → m Protein
- Streptolysin O and S (ASO titres are not used now a days)
- Toxin →
 - 1) Pyrogenic exotoxin
 - 2) Erythrogenic toxin
 - 3) Dick toxin
 - 4) Scarlatiniiform toxin
- Pyrogenic exotoxin C → TSS / Scarlet fever / Necrotising fasciitis
- Streptokinase: DNAase B

Clinical spectrum :

- | | |
|------------------|--------------------------|
| 1) Pharyngitis | 6) Necrotising fasciitis |
| 2) Scarlet fever | 7) TSS |
| 3) Impetigo | 8) myositis |
| 4) Erysipelas | 9) Puerperal sepsis |
| 5) Cellulitis | 10) Otitis media |

Scarlet fever:

00:47:10

- Fever with scarlatiform rash
- upper trunk / Day 2 / Spares palms & soles
- Sandpapper skin
- Strawberry tongue
- Pastia's lines ⊕



Impetigo :

- Superficial infection of skin
- Young children
- Painless
- Erythematous papules / vesicles
- Honeycomb like crusting
- Rx: Benzathine Penicillin

Erysipelas:

- Involves Superficial dermis
- Erythematous edematous plaques
- Tenderness ⊕ ⊕
- Fever ⊕ ⊕ ⊕
- Almost always on face (malar area of face)
- Rx: Benzathine Penicillin

Cellulitis :

- Epidermis + Dermis + Subcutaneous tissue
- mc in Immunocompromised
- Extremely dangerous
- Necrotising fasciitis → Sepsis → Infection Related
(Breach of deep fascia) Glomerulonephritis (IRGN)
↓
RPGN

Necrotizing fasciitis :

- 1) Pain
- 2) Systemic toxicity
- 3) Bullae
- 4) Hyponatremia
- 5) Crepitus
- 6) WBC > 15,000

INFECTIOUS DISEASES – 2

- Empirical therapy targets :

Staph + Strep + Anaerobes



1. vancomycin + Penicillin + Clindamycin
11. Augmentin + cloxacillin (oxacillin) + Clindamycin

Sepsis :

- Old definition → SIRS (Systemic Inflammatory Response Syndrome), a foci of infection in body (Any 2/4 of the following)

1) Temp $< 36^{\circ}\text{C}$ or $> 38^{\circ}\text{C}$

2) TC < 4000 or $> 12,000$

3) HR > 90

4) RR > 24

- New definition:

→ Life threatening organ dysfunction caused by a dysregulated host response to infection

→ SOFA (sepsis organ failure assessment) score – Difficult to calculate

→ qSOFA score

1) Systolic BP ≤ 100 mmHg

2) Altered mentation

3) Respiratory rate $\geq 22/\text{min}$

(score ≥ 2 Poor outcome)

Severe sepsis → 1) Hypotension

(sepsis with 2) Hypoxemia

organ dys- 3) Oliguria

function) 4) Metabolic acidosis

5) Thrombocytopenia

6) Obtundation

Septic shock

00:08:36

- Definition → 1) Septic shock < 90 mmHg for 1 hour despite adequate fluid resuscitation
1) Pressor support needed to maintain BP - $90/70$ mmHg
- Refractory septic shock → Even with Pressor support, BP - < 90 mmHg for 1 hour

Complications :

- 1) Hypotension
- 2) Hyperventilation → Respiratory failure
- 3) DIC
- 4) Adrenal insufficiency
- 5) Septic AKI / ATN
- 6) ARDS

Streptococci viridans

00:13:35

- Species → *S. mutans* / *Sanguis*
- Presents as normal human flora of mouth
- Causes Infective endocarditis
- Penicillin susceptible
- α - hemolytic
- a/w Dental extractions

ENTEROCOCCI:

- γ - Hemolytic
- Normal flora of large intestine
- Needs high salt medium
- a/w large bowel related sepsis
- Hospital acquired infection
- Causes infective endocarditis, meningitis, UTI
- Rx: Vancomycin + Aminoglycoside
- Enterococci are intrinsically resistant to cephalosporins

Infective endocarditis

00:18:30

vegetations consisting of platelets / fibrin / microcolonies on

- 1) Native / prosthetic valve
- 2) low pressure side of VSD
- 3) mural endocardium damaged by foreign body
- 4) Intracardiac devices

- AV shunt infections / Arterio-arterial shunt infections are called **Infective endarteritis**

- MCC overall → **Staph. aureus**

mc community acquired native valve endocarditis →

Strep. Viridans

mc health-care associated native valve endocarditis →

Staph. aureus

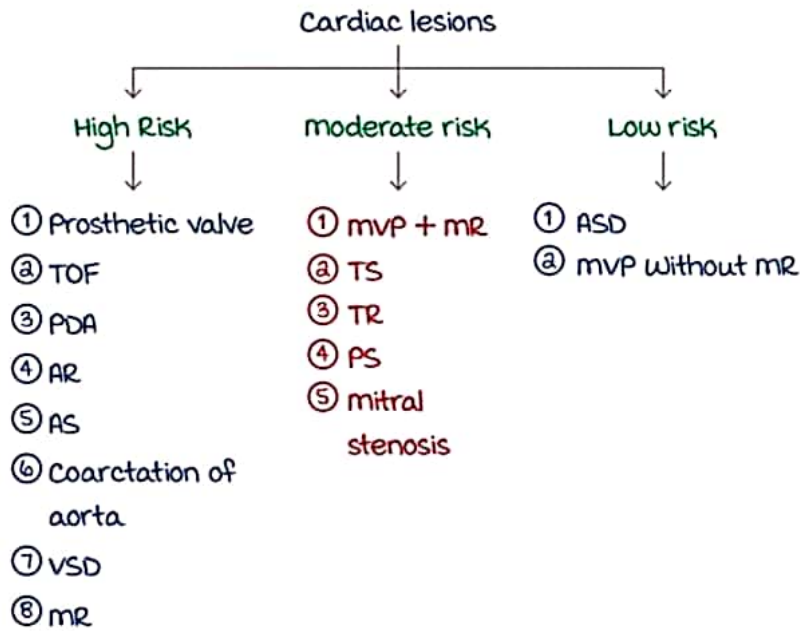
- Prosthetic valve endocarditis:

- 1) < 2 months - **CONS**
- 2) 2 - 12 months - **CONS**
- 3) > 1 year - **Strep. Viridans**

- IV Drug abusers left side - **Staph. aureus / Enterococci**
Right side - **Staph. aureus**

Risk factors:

- 1) IV drug abusers
- 2) CVC (central venous catheter)
- 3) CIED (cardiovascular implantable electronic device)
- 4) Prosthetic valves
- 5) Structural heart disease
- 6) malignancy - **NBTE** (non bacterial thrombotic endocarditis)

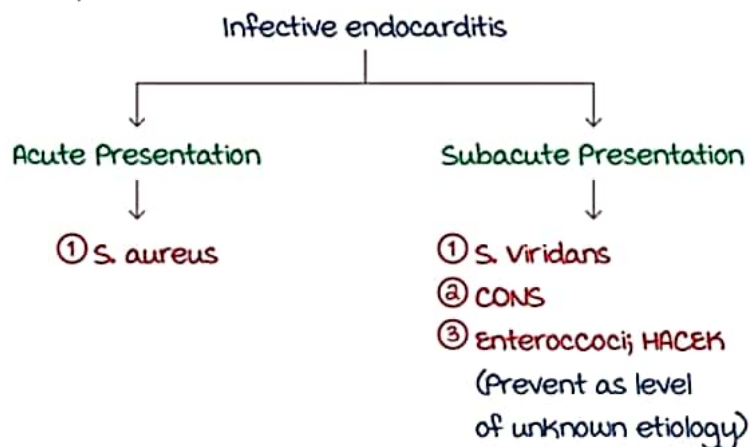


One liners :

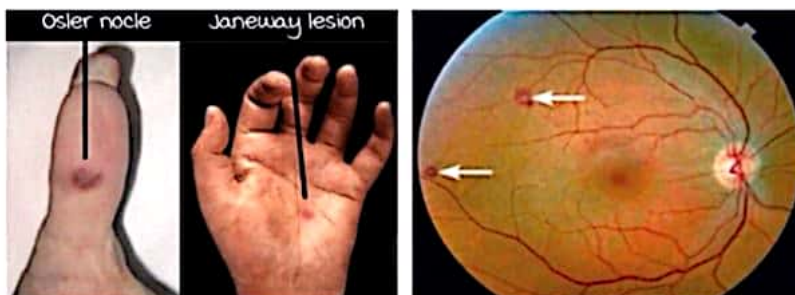
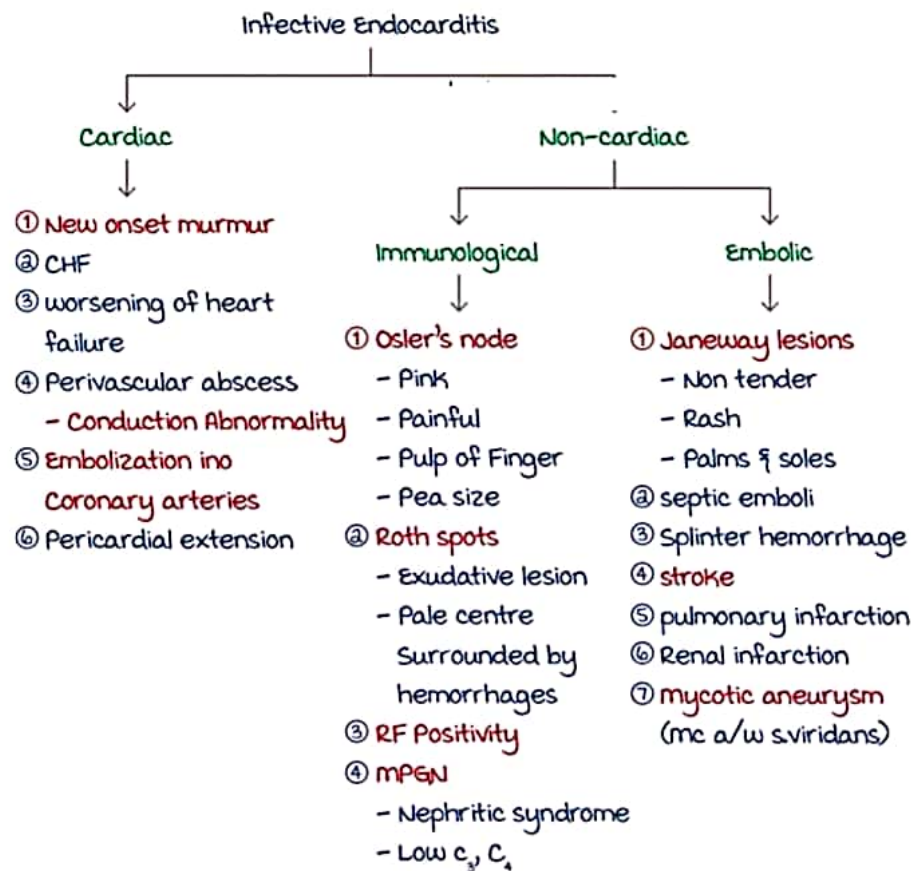
- S. aureus can adhere directly to endothelium without injury
- S. aureus → MCC CIED associated IE
- ASD has least risk of IE among CHD
- 15% of IE have negative blood culture

a) T. whipplei

Clinical presentation:



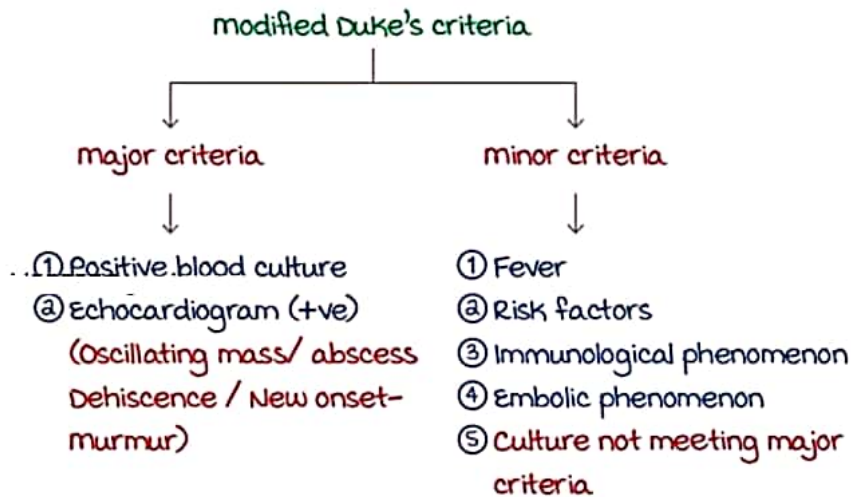
cardinal symptoms- fever, chills, malaise also anaemia



- Infective endocarditis also have;

1) Clubbing

2) Splenomegaly



- Transeosophageal ECHO is needed for:

- 1) myocardial abcess
- 2) valve perforation
- 3) Intracardiac fistula
- 4) Vegetation < 2mm
- 5) Prosthetic valve
- 6) CIED

Summary of treatment

• Streptococci	Penicillin + Gentamycin (2 weeks)
• Enterococci	Ampicillin + Gentamycin (4-6)
• Staphylococci-	
Native valve	Vancomycin (4-6 weeks)
Prosthetic	Vanco + Genta + Rifampicin
Culture negative	Vanco + Gentamicin
Culture report negative	Ceftriaxone + Gentamicin

Surgery in endocarditis:

- 1) Acute heart failure secondary to AR
- 2) Ruptured sinus of valsalva
- 3) Perivascular extension of infection
- 4) Rupture into pericarditis
- 5) Fungal endocarditis

Prophylaxis:

00:58:45

- Needed for
 - 1) Prior endocarditis
 - 2) Prosthetic valve
 - 3) Post cardiac transplant
 - 4) Unrepaired cyanotic congenital heart disease
 - 5) Repaired cyanotic CHD <6 months
(also repaired acyanotic)
- DOC Amoxicillin 2g 1 hour before procedure
 - ↓
 - Allergic to Penicillin
 - ↓
 - Clarithromycin / Clindamycin
- Can't take orally → Ampicillin 2g IV/IM
 - ↓
 - Allergic to penicillin
 - ↓
 - Clindamycin 600 mg IV
- Prophylaxis is also needed in;
 - 1) manipulation of dental tissue / Periapical region /
Perforation of oral mucosa
 - 2) Incision of Respiratory mucosa
- Prophylaxis is not recommended for GI / GU Procedures

HIV – 1

- In 1982 → centers for disease control (CDC) defined HIV as Gay associated virus
- In 1984 → Luc Montagnier isolated virus in Paris (Pasteur institute)
awarded Noble prize in 2008
- Old term → Lymphadenopathy associated virus

HIV – CDC definitive diagnosis (1982):

- Even without laboratory investigations, presence of one of the following itself is enough for diagnosis.

1) Candidiasis of trachea esophagus / Bronchi / Lungs

2) Extrapulmonary cryptococcosis

3) Cryptosporidiasis with diarrhea > 1 month

4) Primary CNS lymphoma <60

5) Kaposi sarcoma < 60

6) PCP Pneumonia

7) Progressive multiple leukoencephalopathy

8) Toxoplasmosis in brain

9) CMV other than liver / spleen / LN

10) HSV infection causing

- mucocutaneous ulcer > 1 month

- Bronchitis

- Pneumonitis

- Esophagitis

11) MAC / M. Kansasii infections involving other than;

- Lung

- Skin

- Lymph node

Staging of HIV based on CD4:

00:10:35

	CD4 count	CD4(%)
Stage 1 →	> 500 cells / μ l	> 26
Stage 2 →	200-500 cells / μ l	14-25
Stage 3 →	< 200 cells / μ l	< 14

Active space

- The above classification is not applicable to children < 1 yr
- In children < 1 yr;

Stage 1 → > 1500 cells / μ l

Stage 2 → 750-1500 cells / μ l

Stage 3 → < 750 cells / μ l

India and HIV:

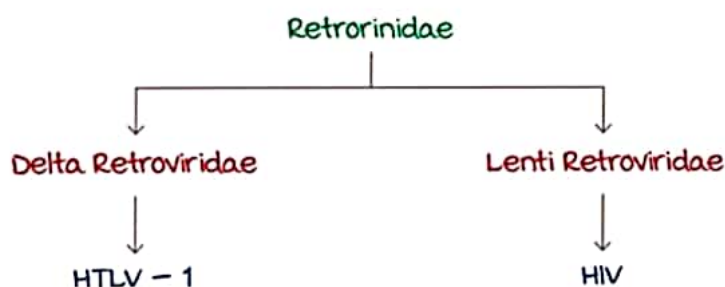
- First case was detected in 1986 in Chennai
- HIV prevalence in India is 0.27%
- Worst affected State → Andhra Pradesh
- maximum prevalence is seen in Manipur
- People living with HIV / AIDS (PLHA) in India is approximately 21 lakhs

one liners:

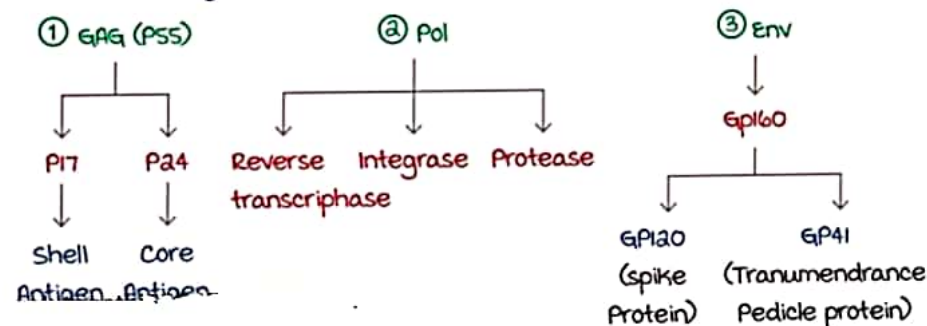
- AIDS can develop within 3 years in 90% with CDA Count < 200/ μ l
- Active replication occurs even when sequestered in lymphoid tissue

Structure of virus

00:16:38



- Structural genes



- Non - structural genes

1) TAT gene (p14)

- Transcriptional activator gene
- Elongation of viral DNA template

2) NEF (p27)

- Negative effector
- Downregulation of CD4 molecules

3) Rev (p19)

- Regulation of viral gene expression

4) Vif (p23)

- Viral infectivity factor

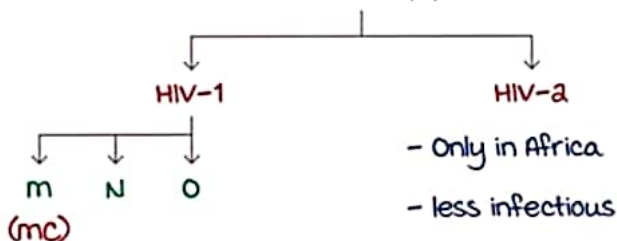
5) Vpr (p15)

- Viral Protein R

6) VPU/VPX

- viral protein u/x

Based on Envelop protein



- most common subtype worldwide - C
- mc subtype in Blood transcription - B
- less virulent
- 11 to Simian virus

- mode of transmission → sexual > parent to child > blood transfusion > needle stick

- risk of transmission → blood transfusion > parent to child > iv drug abuses > needle stick (0.3%)

- chance of infection from female to male is half as from male to female

- maximum risk during pregnancy is not time of delivery (20-30%)

- Exclusive breastfeeding carries low risk of transfusion

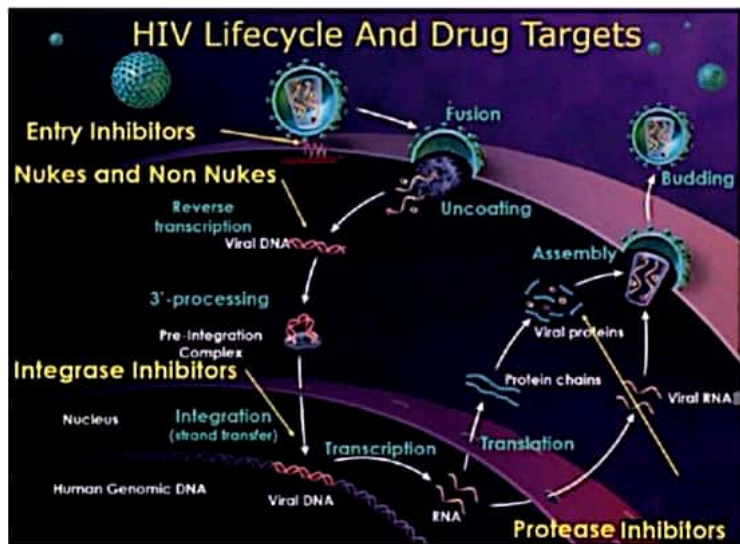
- mastitis, low maternal CD4 count, maternal vitamin A deficiency increases the risk of transmission

- HIV is nil in urine
- Saliva can't transmit HIV because of presence of Salivary Protease inhibitor
- Delta 32 mutation → Don't express CCR5 receptor → protection from HIV infection
- DC sign → C type lectin receptor on dendritic cells → Not protective

HIV life cycle:

- Co- receptor for Fusion of HIV
 - 1) CXCR 4 - T lymphocyte
 - 2) CCR 5 - macrophage

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.



Fusion → uncoating → Reverse transcriptase (Viral DNA)
 ↓
 viral DNA integrated with host DNA ← Integrase
 ↓
 Transcription → Translation → Viral protein assembly (Protease)
 ↓
 Released into circulation ← Budding

- IP → 3-6 weeks
- Presentation similar to infectious mononucleosis;
 - 1) Fever
 - 2) Sore throat
 - 3) Lymphadenopathy
 - 4) 10% meningoencephalitis
- No risk for opportunistic infections
- CD8 T cells upregulated

CD4 count and opportunistic infections:

- < 600 - Lymphadenopathy / thrombocytopenia
- < 500 - Skin infections / HSV / HZV
- < 400 - Kaposi Sarcoma
- < 300 - Oral Hairy leukoplakia / TB
- < 200 - mucocutaneous herpes
 - Cryptosporidium / microsporidium
 - PCP
 - miliary TB
 - esophageal candidiasis
- < 100 - Cerebral toxoplasmosis
 - Cryptococcal meningitis
 - Primary CNS lymphoma
 - HIV associated dementia
 - PMLE
- < 50 - CMV Retinitis
 - MAC infection

CMV infection:

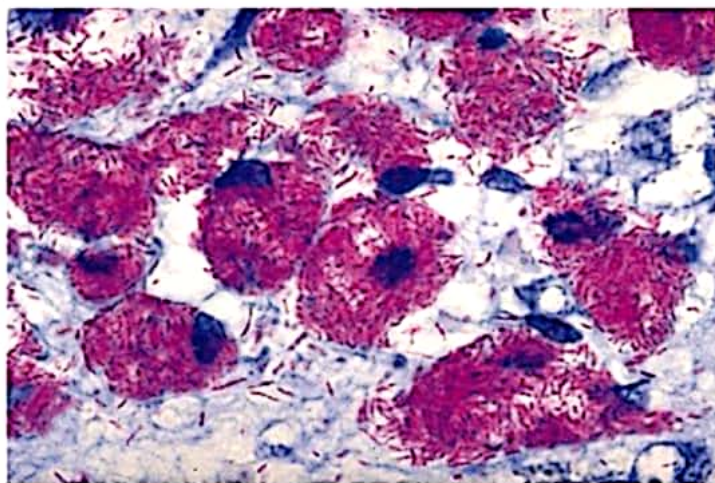
00:50:40

- Retinitis > colitis > esophagitis > pneumonitis
- Retina → Asymmetric bilateral involvement with perivascular hemorrhage or white fluffy exudate
- Painless progressive visual loss
- Rx: IV Ganciclovir x 3 weeks followed by oral Ganciclovir till CD4 > 150 for 6 months

Active space

MAC disease:

- Average CD4 at diagnosis is < 10
- Organism acquired through **Respiratory portal**
- **Disseminated disease** with fever, weight loss, night sweats and lymphadenopathy (**pulmonary involvement is rare**)
- Diagnosis $\rightarrow$ **blood culture / BACTEC** (7 to 10 days)
- Rx : **clarithromycin + Ethambutol**
- Prophylaxis with Azithromycin if $CD4 < 50$



Cerebral toxoplasmosis

00:55:10

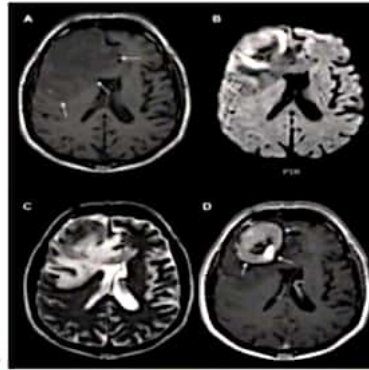
- $CD4 < 100$
- **Reactivation of**
T. gondii cysts in brain
- Fever, headache,
focal neurological deficit,
Seizure & confusion
- MRI $\rightarrow$ **multiple ring enhancing lesions**
- Diagnosis $\rightarrow$ **Elevation of both**
Toxoplasma IgG & IgM
- Rx : Sulfadiazine + Pyrimethamine + leucovorin X 6 weeks
(or) Clindamycin + Pyrimethamine
- Prophylaxis $\rightarrow$ **$CD4 < 100 / \mu l \rightarrow$ Cotrimoxazole**



- *Cryptosporidium parvum*
- Contact → Oocysts in contaminated water
- CD4 < 100
- presents with small bowel diarrhea
- major complication → Biliary involvement & stricturing
- Stool microscopy → 4-6 micrometre
- Acid fast
- Rx: ART + Nitazoxanide

Primary CNS lymphoma:

- AIDS defining malignancy
(example → 1) Kaposi Sarcoma
2) Invasive Ca cancer)
3) primary CNS lymphoma
- EBV associated
- Type → Diffused large B-cell lymphoma
- Rx: Stereotactic RT + methotrexate
- MRI → Hypointense on T₁
Hyperintense on T₂



Fungal meningitis:

- *Cryptococcus neoformans*
- CD4 < 100 cells / μ l
- Best seen with India ink preparation
- Subacute meningitis
- Worsening of headache due to impaired CSF absorption
- CSF study → 1) ↑↑ Opening pressure
2) ↑ Protein
3) ⊖ Sugars
4) Budding yeast hyphae ⊕
- Diagnosis → Latex agglutination test / Cryptococcal antigen test
- Rx: Amphotericin B + 5 Flucytosine
- mode of transmission → inhalation of spores
- Angioinvasion ⊕

- JC virus
- Demyelination of subcortical white matter
- Can occur even when counts > 100-200
- Diagnosis → MRI + JC viral CSF
- No definitive treatment

Pneumocystis jirovecii :

- Opportunistic fungal pulmonary pathogen with no ergosterol, No fungal culture
- Diffuse infiltrates in beginning of parahilar region is seen on chest x-ray
- Beta glucan drive inflammatory response
- Presents with fever / cough / dyspnea especially hypoxia
- Impaired diffusion capacity
- Respiratory alkalosis
- Widened alveola - Arterial desaturation
- Can occur as a part of IRIS
- May be associated with oropharyngeal candidiasis
- Complication → Pneumothorax
- Diagnosis → Indirect immunofluorescence using monoclonal antibodies against Pneumocystis pneumonia.
- Histopathology → Foamy intra alveolar exudates
- methanamine silver stains the wall
- Giemsa wright stains the nuclei
- Doc → Co-trimoxazole, 2nd choice - Trimethoprim + Dapsone,
 - 3rd → Atovaquone
 - 4th → Clindamycin + Primaquine
 - 5th → Pentamidine
- Prophylaxis → Co-trimoxazole > Dapsone > Atovaquone



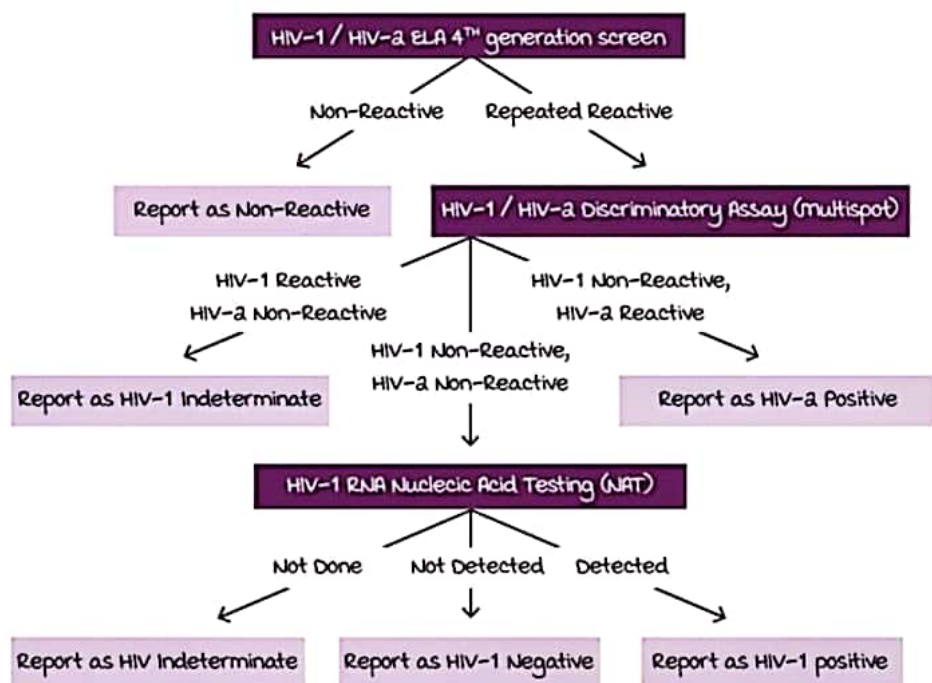
- HHV 8
- may be seen with normal CD4
- multiple vascular nodules in skin, mucous membrane and viscera
- Biopsy → vascular involvement
- Dermatological or visceral lesions managed by chemotherapy (IFN Based)
- milder lesions respond to ART
- Can also occur as part of IRIS

Diagnosis:

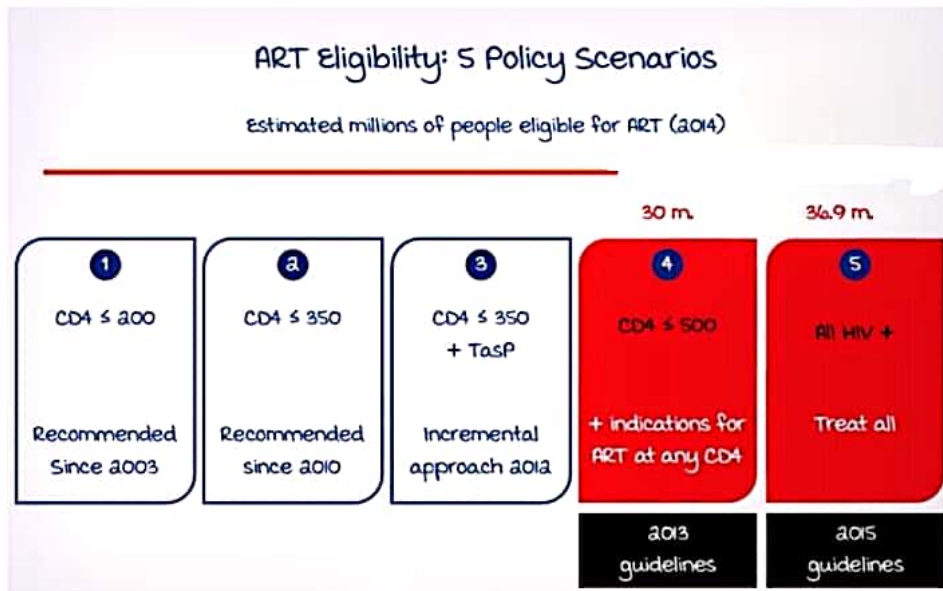


- Screening test → 4th generation ELISA
 - HIV ELISA → 95% positive within 8 weeks; earliest by 22 days
 - Sensitivity of HIV ELISA is 99.99%
 - Supplementary tests:
 - western blot
 - RIPA
 - Line immunoassay
 - IF array
- Specificity - 99.99%

- Indeterminate western blot :
 - Early HIV
 - HIV -2
 - Autoimmune illness
 - Pregnancy
 - Tetanus toxoid
- Gold standard → HIV RNA (detects as early as 12th day)



HIV - 2



All HIV cases are treated irrespective of CD4 count

Classes of HIV drugs:

I. Entry inhibitors $\rightarrow$ Fusion inhibitor $\rightarrow$ **Enfuvirtide** (only injection)
Coreceptor blocker (CCR 5) $\rightarrow$ **maraviroc**

II. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

- 1) Zidovudine
- 2) Didanosine
- 3) Stavudine
- 4) Lamivudine
- 5) Abacavir
- 6) Emtricitabine

III. Non - Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

- 1) Nevirapine
- 2) Efavirenz
- 3) Delavirdine
- 4) Etravirine
- 5) Rilpivirine

IV. Nucleotide Reverse Transcriptase Inhibitor:

Tenofovir

Active space

V. Integrase inhibitor:

- 1) Raltegravir
- 2) Dolutegravir
- 3) Elvitegravir

VI. Protease inhibitor:

- 1) Ritonavir
- 2) Nelfinavir
- 3) Indinavir
- 4) Saquinavir
- 5) Amprenavir
- 6) Atazanavir

- All ART regimen must include Nucleotide Reverse Transcriptase inhibitor → Tenofovir (S/E → Proximal tubular injury → salt wasting Nephropathy → AKI)

- 2nd drug in the Regimen → NRTI.

First zidovudine was used

(A/E → myopathy, Lactic acidosis,
BM Suppression, Resistance)



Changed to Didanosine

(A/E → Pancreatitis)



Changed to Stavudine

(A/E → Peripheral Neuropathy)



Drugs used now → Lamivudine, Abacavir,
Emtricitabine

- Abacavir-- requires HLAB5701 testing prior to administration
(due to risk of hypersensitivity & sudden MI) 3rd drug → NNRTI
→ Efavirenz (A/E : Delusions & CNS toxicity)

- NACO Protocol → Tenofovir + Lamivudine + Efavirenz

- World wide Recommended protocol → Tenofovir

+

Emtricitabine

+

Integrase inhibitor (Raltegravir)

- Protease inhibitor is not used as first-line → metabolic Syndrome complex
- Resistance testing is mandatory
- **Primary goal of therapy** (viral load <20 copies /ml)
- 3 drugs from 2 different classes must be used

One liners :

- PCP Pneumonia - DOC --> Cotrimoxazole
- MAC infection - DOC --> Ethambutol
- Toxoplasmosis - DOC --> Sulfadiazine + Pyrimethamine
- Any patient with HIV +ve should undergo tuberculin skin test, if positive should receive Isoniazid for 9-12 months
- DOC for Cryptosporidium parvum - Nitazoxanide
- Perivascular hemorrhages and retinal exudates - CMV retinitis
- Characteristic cells of CNS involved in AIDS - microglial cells
- mc extranodal site of lymphoma → **Brain**
- Commonest helminthic infection → **Strongyloides stercoralis**
- **microglial cells** are characteristically involved
- Nevirapine → **Hepatotoxicity/Rash**
- **Delavirdine** is least preferred → **Because of multiple daily dosing**
- Prior NNRTI resistance → **Only Etravirine can be used**
- **Ritonavir boosting** is recommended for all **except Nelfinavir**
- All protease inhibitor is associated with metabolic Syndrome **Except Atazanavir**
- Amprenavir → **Hyperbilirubinemia**
- NNRTI, are **ineffective** against HIV -2

HIV -2 NACO Regimen → Tenofovir

+

Lamivudine

+

Lopinavir / Ritonavir

Best Regimen → Tenofovir

+

Emtricitabine

+

Dolutegravir

Needle stick injury prophylaxis :

- Optimally effective if started within 72 hours
- Tenofovir + Emtricitabine + Dolutegravir X 4 weeks (ANRTI's + Integrase inhibitor)
- Abacavir and Nevirapine are always avoided
- Pre-exposure prophylaxis → Emtricitabine / Tenofovir

SLE - ETIOPATHOGENESIS

Connective tissue disorder

00:00:08

- 1) SLE
- 2) APLA
- 3) Sjogren
- 4) Polymyositis / Dermatomyositis
- 5) mixed connective tissue disorder
- 6) Sarcoidosis

Rheumatoid Arthritis can be considered as Arthritis

Vasculitis

Connective Tissue Disorder

SLE

00:05:24

Systemic lupus Erythematosus

Disease of females in reproductive age group

(F:m → 9:1)

male SLE - Poor Prognosis

Childhood SLE : 100% Renal involvement

Type 3 HSR (Immune complex mediated disease)



- Deposited in
1. Vessel wall: Vasculitis
 2. Joints: Arthritis
 3. Glomeruli: Glomerulonephritis

Other Eg: Of Type 3 Hypersensitivity reaction :

- 1) PAN
- 2) Reactive Arthritis
- 3) PSGN

1. Genetic susceptibility - must to be detected

1) most strongest genetic risk of SLE : Early Complement deficiency

C_1q, C_2, C_4

(most important - C_1q deficiency)

Active space

[C₅b - C₉ (late complement deficiency)
- Susceptibility to Neisseria, Toxoplasma]

2) HLA DR-3, DR-2, B8

3) TREX gene mutation (present on chromosome)

II Environmental risk factor (2nd hit)

1) EBV

2) OCP & HRT

3) Smoking (Alcohol is protective)

4) Deficiency of Vit D

5) Silicosis

UV - B rays do not trigger SLE
it can cause flares in an SLE patient]

Genetic + environmental



Immune dysregulation



↑ Apoptosis & reduced clearance of
apoptotic cell (Innate immunity is activated)

Key pathogenic cytokine: IFN - α

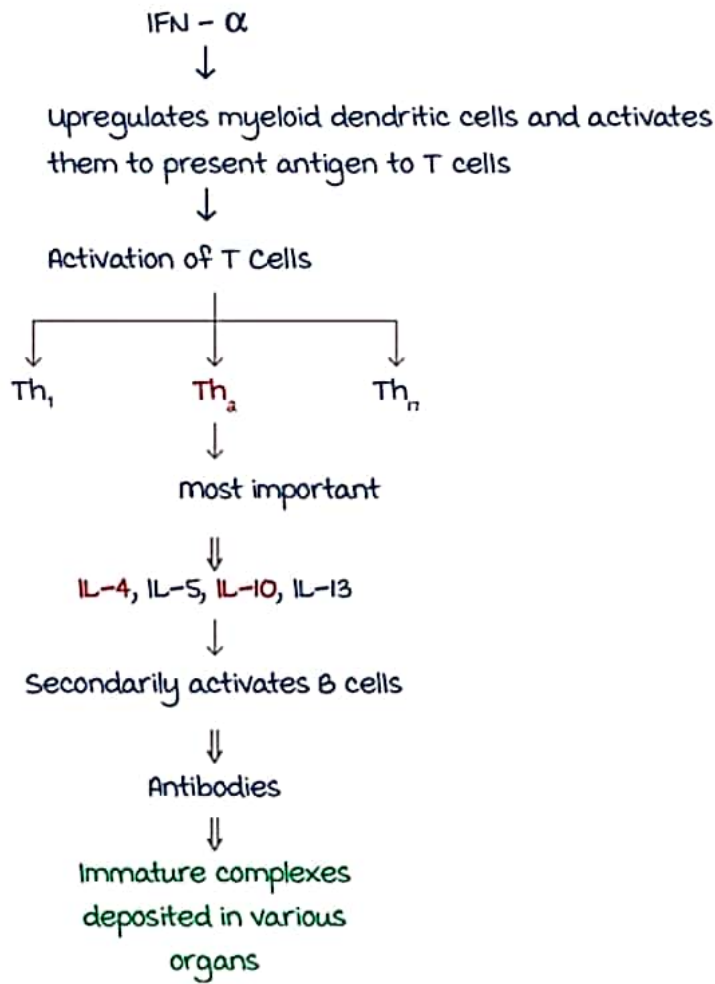


Produced by
Lymphoid dendritic cell
(plasmacytoid dendritic cell)

Genetic signature of SLE: upregulation of genes due to IFN - α

[IFN - β - Produced by Fibroblast

IFN - γ - Produced by TH1 (adaptive immunity)]



Activation of B cell

00:24:20

T cell activates B cell by:

- I. IL-4 Pathway
- II. CD40 L - CD40 interaction

↓

T cell

↓

B cell
- III. IL-12/21 pathway

SLE- IMMUNOLOGICAL BASIS

Antibodies

00:00:08

Auto antibodies may be seen 3 year before the onset of clinical feature

Screening → ANA (Anti Nuclear Antibody)



Also used for all connective tissue disorder screening

ANA positivity is only significant if done by

Indirect immunofluorescence using Hep-2 cell line

(Hep - 2 → Human epidermoid cell line)



Quantitative result

(ELISA is qualitative and is not significant)

Titre $\geq 1/160$ is significant ($< 1/80$ insignificant) can be due to

- 1) infection
- 2) Normal ($< 5\%$)
- 3) Thyroid disorder
- 4) Inflammatory bowel disease

[SLE - 97 to 98% ANA+ve

Scleroderma - 95% ANA+ve

Sjogren - 95% ANA+ve

mixed connective tissue disorder (MCTD) - 100% ANA+ve]

If ANA (+ve)

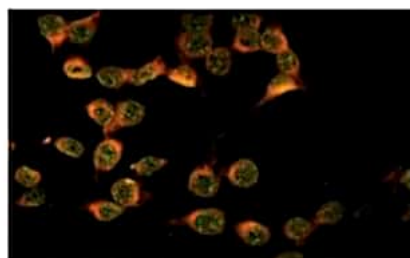


ANA positivity



1) **Speckled pattern**: most suggestive of connective tissue disorder but non-specific

Anti-Nuclear Antibody (ANA)
speckled pattern



Active space

- 2) Rim pattern - SLE
- 3) Homogenous - Drug induced SLE
- 4) Nucleolar pattern - Scleroderma
- 5) Centromere pattern - CREST syndrome

ANA (+ve)
↓
ENA profile (Extractable Nuclear Antigen Profile)
1) Anti ds DNA (70-75% of SLE patient)
2) Anti smith (20-25% of SLE patient)

Anti smith is more specific

But - Anti ds DNA is still preferred because:

- ⊕ in 70-75% of SLE patients
- High titre correlate with disease activity
- ↑ Chance of nephritis & vasculitis

• Anti-dsDNA, ↓ C₃, ↓ C₄ - Correlate with disease activity
↓
Due to activation of classical complement pathway

3) Anti U1 RNP

Overlap Syndrome: Features of SLE / Limited sclerodermas / Polymyositis / Dermatomyositis ± RA

For eg: SLE/Scleroderma overlap:
- Predominant is written 1st
- In this case, SLE is predominant

mixed connective tissue disorder
= Overlap syndrome + Anti UIRNP

Mixed connective tissue disorder v/s overlap 00:16:30

Active space

mCTD	Overlap
1) SLE / Scleroderma Overlap + Anti UIRNP	SLE / Scleroderma overlap with Anti UIRNP (-ve) ↓
2) Doesn't behave like SLE or Scleroderma but have entirely different presentation	Behave like SLE or scleroderma

3) Associated with Raynaud's phenomenon

4) ILD

5) Absence of Renal involvement

6) 100% ANA +ve

4) Anti Ro (SS-A) , Anti La (SS-B)

Associated with 2° sjogren's

Pregnancy - Neonatal lupus with congenital heart block

Titres correlate with ↓ risk of nephritis & vasculitis associated with subacute cutaneous lupus (High photosensitivity skin lesion)

6) Anti histone antibody

- Drug induced lupus

7) Anti phospholipid antibody (APLA)

- APLA syndrome

- 1/3rd SLE patients have APLA

8) Anti erythrocyte antibody

- SLE patients are prone for Auto-immune hemolytic anemia (AIHA)

9) Anti platelet antibody

- Associated with 2° idiopathic thrombocytic purpura (ITP)

10) Anti neuronal (glutamate) antibody

- m/c antibody in CNS / Neuronal lupus

11) Anti - ribosomal P antibody

- Specific for depression / psychosis in CNS lupus

m/c CNS lesion: Decline in cognitive function

SLE : CLINICAL FEATURES

Clinical presentation

00:01:12

Associated symptoms with SLE:

- Fever of unknown origin
- Fatigue / tiredness / lethargy
- Irregular cycle / weight gain
- Unexplained hair loss or dryness of skin

Skin presentations are:

- 1) Acute cutaneous Lupus Erythematosus (malar Rash)
- 2) Chronic cutaneous Lupus Erythematosus (Discoid Rash)
- 3) Subacute cutaneous Lupus Erythematosus

Acute cutaneous lupus erythematosus

00:03:10

Also Known as **malar Rash**

- MC rash SLE
- Highly photosensitive
- Erythematous Rash
- Tendency for scaling
- Non-scarring
- Spares nasolabial fold

DD: Acne Rosacea



Chronic cutaneous lupus erythematosus

00:05:20

Also Known as **Discoid Rash**

- most common disfiguring rash
- Erythematous rash involving face, scalp, neck & back

Biopsy findings are:

- 1) Keratotic scaling
- 2) Follicular plugging
- 3) Dermal atrophy



Seen as circular erythematous patches
(hyperpigmentation at borders)

5-20 Rule:

Patient with Discoid Rash → Chances of SLE: 5%

Patient with SLE → Chances of discoid rash (20%)

It's a Premalignant Lesion → Squamous cell carcinoma of skin
(∴ biopsy is a must)

SLE generally cause Non-scarring alopecia

But Discoid Lupus Erythematosus (DLE) → Scarring cicatricial alopecia

Discoid lesions on back



Carpet Track sign of DLE



Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Subacute cutaneous lupus

00:10:32

In subacute cutaneous Lupus – 50% SLE

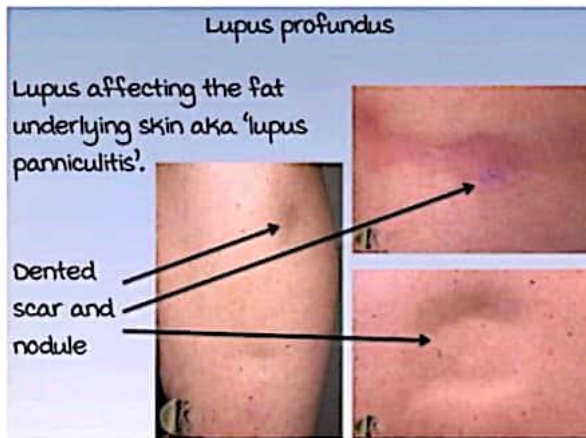
- Highly photosensitive
- Superficial
- Non-scarring
- B/L symmetrical
- Seen in forearm
- Psoriasiform pattern
- Associated with Anti Ro/La antibodies
- Precipitated by : : Hydrochlorothiazide



Lupus profundus

Also known as Lupus panniculitis

Affects the fat underlying the skin



Verrucous Lupus

Also Known as Hypertrophic Lupus



Arthritis in SLE

00:13:46

1) Presents as arthritis and not arthralgia

Arthralgia – Only pain

Arthritis – Evidence of inflammation
(redness, edema, warmth, tenderness)

2) It is an inflammatory Arthritis

- Relieved with activity & exacerbated with rest

- ↑ ESR, CRP ↓

↳ CRP levels low because of anti CRP antibodies

- Synovial fluid WBC ↑↑ (>500/mc)

3) B/L symmetrical

4) Small joint polyarthritis

5) Predominant upper limb arthritis

6) Non deforming, non erosive

Jaccoud Arthropathy



SLE arthritis which is
deforming but non-erosive

If erosive - Do anti CCP



Suspecting RA



Whenever one joint swelling is out of proportion:

→ Eg: 3 days h/o fever on & off, pain, swelling & edema of
knee joint, asymmetrical, severe tenderness

- Septic Arthritis

Patient on 3 months steroid develops progressive pain on hip
movement especially on flexion & internal rotation



Suspect Avascular necrosis / Osteonecrosis

ORGAN SYSTEM MANIFESTATIONS OF SLE

Vascular manifestations

00:00:22

- m/c cause of death in SLE: Acute coronary syndrome
- Condition of vessel in SLE affected 30 year old resembles vessel in an 80 year old unaffected woman.
- Accelerated atherosclerosis in SLE
= MI Equivalent
- APLA is seen in $\frac{1}{3}^{\text{rd}}$ patient
- Also associated with small vessel vasculitis



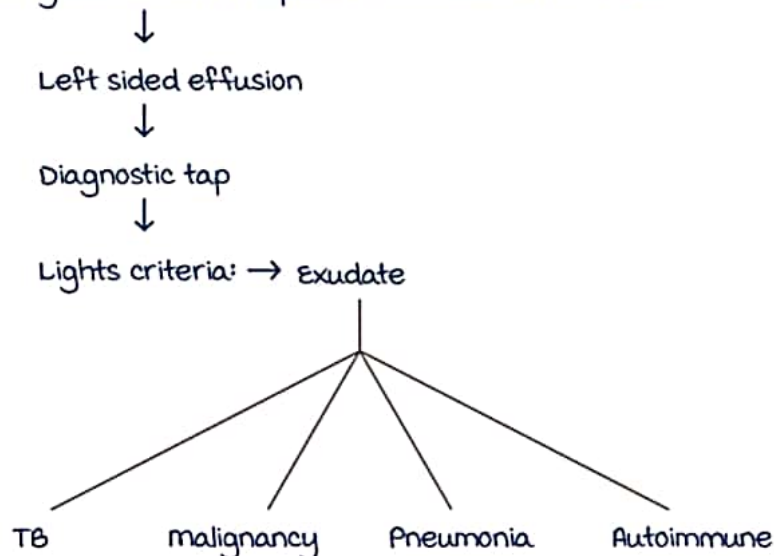
Lung

00:03:28

1) pleuritis $\pm$ effusion

- m/c Lung involvement
- small, B/L exudative effusion

Respiratory discomfort in a patient on treatment for SLE



Active space

Autoimmune causes- diagnosis of exclusion

a) Lupus Pneumonitis (Diffuse alveolar hemorrhage)

30 yr female under treatment for SLE (6 months) in remission phase with minimal steroid dose. Presents acutely with 3 days fever, cough, 2-3 episodes of hemoptysis, Hemodynamically stable

D/D Could be community acquired pneumonia



↓
R_x with antibiotics

Or

SLE relapse → Lupus pneumonitis

↓
R_x with Immunosuppressants

Assess disease activity: ds - DNA titres

C3, C4 - in SLE

CRP ↓↓

Diffuse alveolar hemorrhage - s/o SLE

1) Hemosiderin laden macrophage in sputum

2) PFT : ↑ DLCO

3) Bronchoscopy - Blood on air passage

3) Interstitial Lung Disease

- Very minimal

- Presents as Non - Specific interstitial pneumonia

4) Shrinking Lung Syndrome

- Restrictive ventilator defect

- Elevated hemidiaphragm + Shrunk lung

- Nerve involvement

Heart - manifestations

00:14:59

m/c Cardiac lesion : Pericarditis without tamponade
(postmortem findings)

m/c endocarditis : Libmann sachs endocarditis (vegetations on
the under surface of valve leaflet)

m/c valvular : mitral Regurgitation

m/c arrhythmia : Ventricular Tachycardia

GIT - manifestations

00:16:46

m/c manifestation : Decreased peristalsis with preserved LES tone

m/c liver manifestation: Raised enzymes (clinically not significant)

Autoimmune hepatitis type 1 - Lupoid hepatitis

CNS - manifestations

00:18:06

m/c manifestation: ↓ cognitive function

Aggressive CNS Lupus - Diffuse grey matter lesions and seizures.

Antibodies: Antiglutamate antibody

Antibodies on depression or psychosis : Antiribosomal P

Increased risk of stroke/CVT in SLE associated with APLA

Hematological - manifestations

00:20:24

m/c clinical manifestation : Anemia of chronic disease

m/c Lab abnormality: Lymphopenia

1) Autoimmune hemolytic anemia:

Any young female with a rapidly progressive anemia

Look for features of hemolysis :

Reticulocyte > 2.5

macrocytes

↑ LDH

↓ haptoglobins

Jaundice

↑ Indirect bilirubin

Splenomegaly

§ do DCT

In SLE,

Warm antibody (IgG) mediated DCT +ve AIHA (extravascular)

a) a° ITP :

Due to antiplatelet antibody

SLE is premalignant → DLBCL (Diffuse large B-cell lymphoma)

TABLE : Systemic Lupus International Collaborating Clinic criteria for Classification of Systemic Lupus Erythematosus

CLINICAL MANIFESTATIONS	IMMUNOLOGIC MANIFESTATIONS
Skin Acute , subacute cutaneous LE (photosensitive, malar, maculopapular, bullous) Chronic cutaneous LE (discoid lupus, panniculitis, lichen planus-like, hypertrophic verrucous, chilblains) Oral or nasal ulcers Nonscarring Alopecia Synovitis involving ≥ 2 joints Serositis (Pleurisy, pericarditis) Renal Prot/cr ≥ 0.5 RBC casts Biopsy Neurologic Seizures, psychosis, mononeuritis, myelitis, peripheral or cranial neuropathies, acute confusional state Hemolytic anemia Leucopenia ($< 4000/\mu\text{L}$) or Lymphopenia ($< 1000/\mu\text{L}$) Thrombocytopenia ($< 100,000/\mu\text{L}$)	ANA $>$ reference negative value Anti - dsDNA $>$ reference, if by ELISA $2\times$ Reference Anti-sm Antiphospholipid (any of lupus anticoagulant, false-positive RPR, anti-cardiolipin, anti-β glycoprotein I) Low serum complement (C3, C4, or CH50) Positive direct coombs test in Absence of hemolytic anemia

Renal biopsy read as systemic lupus qualifies for classification as SLE if any lupus autoantibodies are present, even if total criteria are fewer than 4

Renal - manifestations

00:28:13

Lupus Nephritis Glomerular involvement

- 50 to 60% SLE patients have renal involvement
- Children - 100%

Class I : minimal mesangial Lupus

Class II : mesangial Proliferative Lupus

- Benign
- Not associated with disease activity
- asymptomatic
- doesn't require treatment
- Immune complex deposition in both

Class I

Class II

Light microscopy: Normal

mesangial Proliferation

Immunofluorescence : mesangial Immune complex deposits in both

Biopsy is done when : **Proteinuria** > 500 mg/day with
microhematuria
Proteinuria > 1 g/day

Active Lupus Nephritis: Class III (< 50% glomerulus involved)
Class IV (> 50% glomeruli involved)

Class III : Focal Proliferative Lupus Nephritis

Class IV: Diffuse Proliferative Lupus Nephritis

Class IV : Worst prognosis

Presentation :

Acute onset rapidly progressive renal failure

Proteinuria + RBC in urine

Crescents on Biopsy – Type II RPGN

anti ds-DNA high

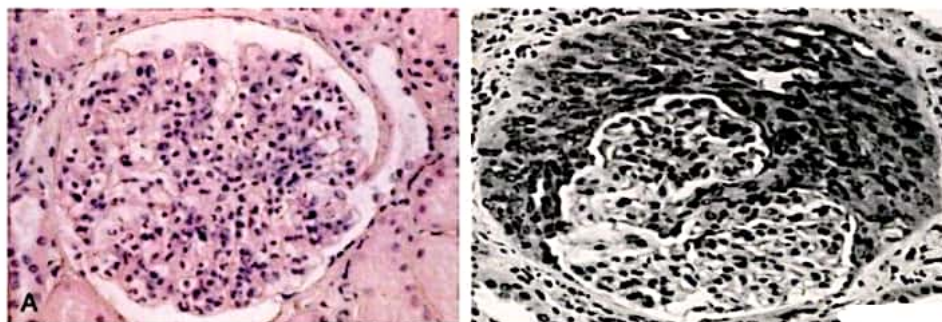
c3,c4 and CRP low

Class IV:

RPRF → RPGN presentation (type II)

Light microscopy

- **DPGN + Crescents**



Immunofluorescence:

most specific pathologic finding of SLE

Full house effect

- IgG + IgM + IgA + C₃ + C₄ + C1q

(wireloop lesion –class IV– subendothelial deposits – non specific)

Electron microscopy: Hematoxylin bodies

Class I & class II are treated when there is Nephrotic syndrome

Known as **Lupus podocytopathy**

Class V – membranous Lupus

Adult onset Nephrotic syndrome

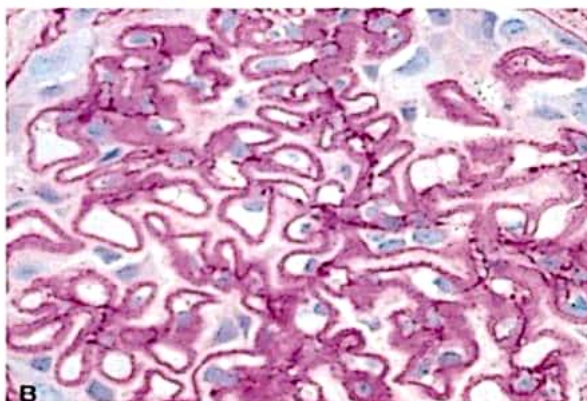
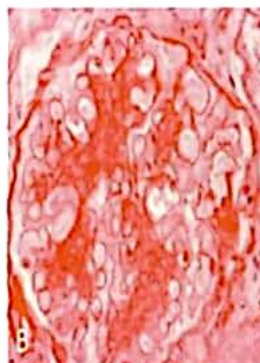
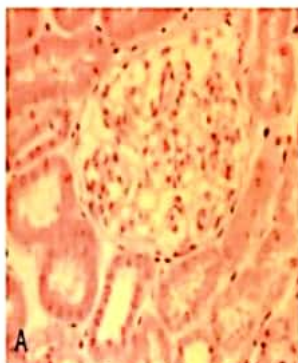
Biopsy : membranous nephropathy

Light microscopy: ↑ capillary wall thickness

IF: Immune complex deposits in the capillary wall

Em : Subepithelial deposits

- refractory to standard therapy



Class IV

Activity index:

1. PMN infiltrates
2. Karyorrhexis
3. Wire loop lesions
4. Endocapillary hypercellularity
5. New cellular crescents
6. Degree of interstitial inflammation

Chronicity index:

- Tubular atrophy
- Interstitial fibrosis
- Fibrous crescents

Class VI : Advanced sclerotic lupus

> 90% of

Glomeruli are sclerosed

MANAGEMENT OF SLE

Management based on skin & joint involvement

00:00:30

mild → Topical steroids

moderate / severe → Topical steroids + Hydroxychloroquine

[Antimalarial]



S/E - Irreversible retinal

Toxicity [1%]



No response



Oral methotrexate

Second line drugs:

Retinoids

Thalidomide

Management based on Organ system involvement

00:02:19

Steroids → I.V methyl prednisolone (500 mg - 1 g) followed by

Oral prednisolone (1 mg/kg/day)



Taper and bring to minimal 5 mg/day dose
Over a period of 4 months [3-4]



Plus cyclofosfamide or mmF [equally effective]

CYCLOFOSFAMIDE:

According to NIH protocol: 6 doses of I.V Cyclofosfamide
monthly once - Ig IV

According to Euro-lupus protocol: [low dose]

500mg I.V every 2 weeks
X 3 months

Active space

adverse effects :

- a] Secondary malignancy - AML
- b] gonadal toxicity - Ovum banks
- c] Haemorrhagic cystitis

Dose dependent toxicity - Bone marrow suppression

mycophenolate mofetil:

IMP dehydrogenase inhibitors

Purine synthesis inhibitors

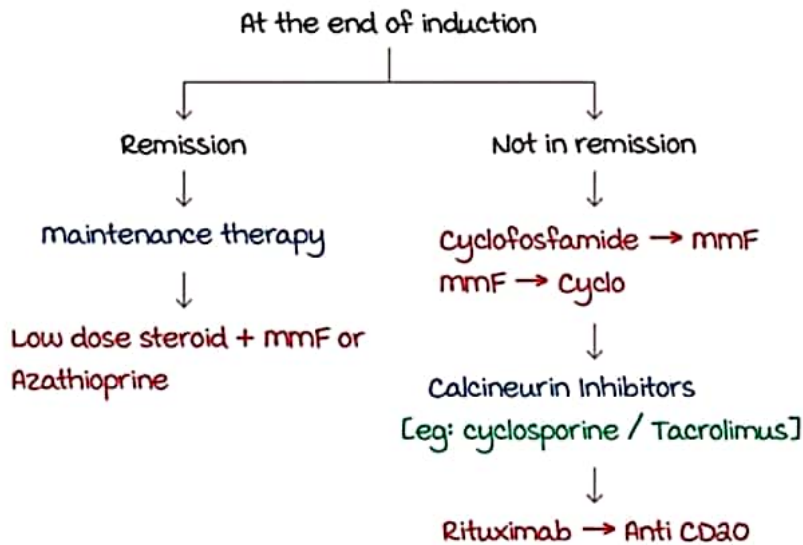
Dose: 500 mg 1-0-1 X 1 week

Ig 1-0-1 X 1 week

1.5g 1-0-1 X 22 week

Total : 6 months therapy

Side effects: GI side effects; Bone marrow Suppression [less]



Treatment of class V lupus

00:08:59

- [Steroid refractory]

mmF + Steroid [steroid refractory]



Anifrolumab – Against IFN α [Not available in india]

Anti CD20 – Rituximab; Ocrelizumab

CTLA4 -Ig – Fusion molecule- [Abatacept]
(Fc Ig4)

Anti CD22 – Epratuzumab

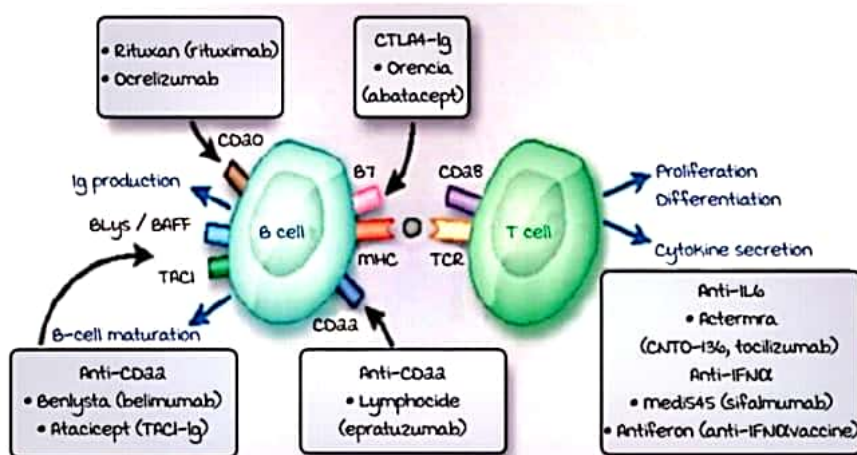
Anti BLys – Benlysta [Belimumab]
↓
Atacicept [TACI -Ig]

[B -lymphocyte
Stimulation]

Anti IL -6 – Tocilizumab

Anti -INF α – Sifalimumab

Antiferon [anti -IFN α vaccine]



Drug induced SLE

00:12:58

C Carbamazepine; chlorpromazine

H Hydralazine

I Isoniazid; Interferon; Infliximab

m methyl dopa

P Procainamide ; Phenytoin; Propyl thiouracil

- m : F $\Rightarrow$ 1 : 1

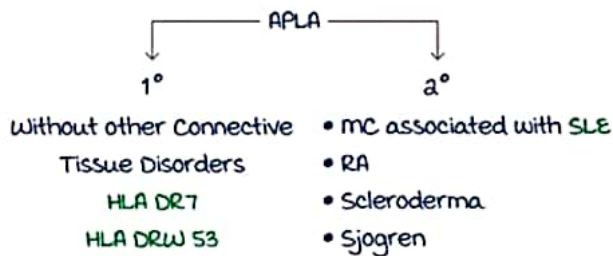
- Skin and joints $\rightarrow$ Always involved

- Kidney and brain never involved

- Anti ds DNA negative
- Anti histone positive
- ANA – homogenous pattern
- most drugs causing lupus are safe in SLE patients
- On stopping drugs – very good prognosis

APLA

Anti phospholipid antibody syndrome



- Characterized by antibodies acting on Protein C & Inhibiting it
- Function of protein C - Inhibits Factor 5 & 8



In APLA → Uncontrolled activation of Factor 5 & 8



Predisposition to thrombosis

- Abs acting on platelets
 - Thrombocytopenia
 - Platelet count < 1,00,000/ml
 - Not low enough to produce bleeding
 - Thrombocytopenia without bleed + thrombosis ⇒ APLA
- DD: Heparin

- Target Antigens in APLA - β_2 glycoprotein
- Phospholipid
- Prothrombin

Lab criteria: Any 1 out of 3 Abs +ve twice over 12wks

1. Anti cardiolipin Ab

- IgG Ab - Done by ELISA
- most sensitive

2. Anti β_2 gp Ab

- IgG, IgM, IgA
- ELISA

Active space

3. Lupus Anticoagulant

- most specific
- Detected indirectly by the prolongation of :

- aPTT
- DRVVT (Diluted Russell Viper Venom Test)
- KCT (Kaolin Clotting Time)

Clinical criteria :

Pregnancy criteria: Any 1 out of 3 +ve

- Before 10wks - 3 or more miscarriages
- After 10wks - Even 1 miscarriage (2nd Trimester Abortion)
- Premature Delivery (<34 wks) of a morphologically normal neonate due to Preeclampsia / Eclampsia / HELLP Syndrome

Adult criteria :

- Episode of Thrombosis with Ab +ve - most often venous thrombosis
 - DVT (MC cause)
 - Venous obstruction causing venular dilation - Lacy network pattern or Livedo reticularis
 - Pulmonary embolism
- Arterial Thrombosis:
 - Stroke (mc)
 - Cardiac - MI/Libman sacks
 - Retinal artery thrombosis

Livedo reticularis



- Neurological Symptoms in APLA: chorea
migraine can occur
- Rarely involves Renal vein / Small vessels in kidney to produce Thrombotic microangiopathy
- Adrenal vessels: Addison's like picture if Adrenal vessels are involved

6. AIHA with Thrombocytopenia & no bleed

Revised sapporo classification criteria for apla

Clinical Criteria :

1. Vascular thrombosis

One or more clinical episodes of arterial venous or small vessel thrombosis in any tissue or organ

2. Pregnancy morbidity

- (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
- (b) One or more premature births of a morphologically normal neonate before 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency or,
- (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory Criteria

- 1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis
- 2. Anticardiolipin antibody of immunoglobulin (Ig) G or IgM isotype in serum or plasma, present in medium or high titer (>40 GPL or MPL, or > 99th percentile), on two or more occasions at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA)
- 3. Anti β_2 glycoprotein I antibody of IgG or IgM isotype in serum or plasma (in titer > 99th percentile) present on two or more occasions at least 12 weeks apart, measured by a standardized ELISA

Definite antiphospholipid syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met . Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive antiphospholipid antibody test and the clinical manifestation

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above

TABLE CLASSIFICATION AND NOMENCLATURE OF ANTIPHOSPHOLIPID ANTIBODIES		
Name	Assay for their Detection	Comments
Antibodies against cardiolipin (aCL)	Enzyme-linked immunosorbent assay (ELISA) using as antigen cardiolipin (CL), a negatively charged phospholipid	aCL from patients with APS recognize β_2 GPI existing in the humans bovine serum, which is used to block the nonspecific bindings sites CL simply stabilizes β_2 GPI at high concentration on the polystyrene
Antibodies against β_2 GPI (anti- β_2 GPI)	ELISA using as antigen affinity purified or recombinant β_2 GPI in the absence of PL	Antibodies recognize β_2 GPI bound in the absence of CL to an oxide surface, where oxygen atoms in the moieties C-O or C=O were intra-irradiation
Lupus anticoagulant (LA)	Activated partial thromboplastin time (aPTT) Kaolin clotting time (KCT) Dilute Russel viper venom test (DRVVT)	Antibodies recognize β_2 GPI or prothrombin (PT) and elongate aPTT, interfere with the generation of thrombin by prothrombin, and LA induces thrombosis in viv

Abbreviations: APS: antiphospholipid syndrome, β_2 GPI: β_2 glycoprotein I, PL: phospholipid

Clinical features:

1. DVT/BCS >> Arterial Thrombosis
2. Hepatic vein Thrombosis - Budd chiari syndrome may be seen rarely
3. Sneddon syndrome - Livedo reticularis + HTN + stroke
4. Renal site of lesion - Small vessels
5. AIHA + Thrombocytopenia without bleeding
6. Adrenal dysfunction
7. Lupus Anticoagulant positivity has the Highest risk of thrombotic events specific / +ve in 40% cases
8. ACL Ab is most sensitive
9. IgA Ab / β_2 gpAb

Catastrophic APLA syndrome

00:13:45

- Occurs in patient with APLA with a trigger - most often an infection
- Defined as ≥ 3 organ systems getting involved in 21 week $\ddagger$
Histologically small vessel occlusion with lab finding of APLA

Treatment of APLA

00:14:56

In pregnancy

Previous H/O Thrombosis
due to APLA

(or)

H/O miscarriage

(or)

Preterm Delivery due to
APLA

↓

Heparin + Low dose
Aspirin through out
Pregnancy
+

Warfarin - Post partum &
continued for life if
documented evidence of
APLA is established

In Adults

- APLA Diagnosed due to
Thrombosis

↓

LMW Heparin x 5 days
overlapped with
warfarin for life (INR 2-3)

- Recurrent thrombosis -
INR 2.5-3.5

- APLA diagnosed laboratory
wise but No clinical signs
⇒ No 1° prophylaxis required

- Anyone with H/O Thrombosis in
1st Pregnancy / Anyone with
H/O Thrombosis ⇒ Requires
Heparin + Low dose Aspirin
in Pregnancy &/b Warfarin
irrespective of APLA status

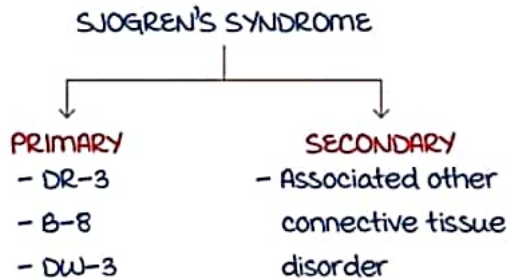
Catastrophic APLA R_x: Requires I.V Ig + Plasmapheresis

- STEROIDS ARE USELESS IN APLA except in catastrophic APLA where
I.V steroids may be tried

SJOGREN'S SYNDROME AND SYSTEMIC SCLEROSIS

Sjogren's syndrome

00:01:05

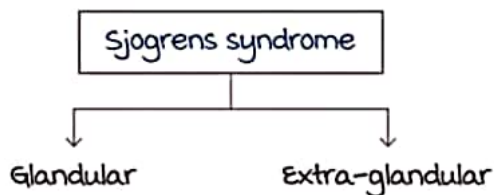


Sjogren's syndrome:

- 9 : 1 [Female : male]
- middle aged and elderly females
- 40-60 years - [Peak age]

Causes for secondary sjogrens syndrome:

1. mc cause → Rheumatoid arthritis*
2. Systemic lupus erythematosus (SLE)
3. Scleroderma
4. mixed connective tissue disease (CTD) (mCTD)
5. Primary biliary cirrhosis
6. Chronic hepatitis-c [always associated]
7. Vasculitis



Glandular sjogren's

00:04:03

- Dry mouth [xerostomia] [more specific]
- Dry eye
- Fatigue; Anaemia of chronic disease
- Deep red tongue
- Dental caries



Bilateral parotid
enlargement – primary
sjogren's syndrome



Schirmer test:

Detects deficient
tear production in
sjogren's syndrome
-decreased tear break up time



Extraglandular sjogren's

00:06:01

m/c manifestation – Arthritis of SLE & Sjogren's are similar

Raynauds phenomenon – 2° Raynauds

1) Lung involvement – small airway pathology

Interstitial lung disease(ILD) – more common

Non – specific interstitial pneumonia(NSIP) – m/c lung manifestation

most characteristic → Lymphocytic Interstitial pneumonia(ILP)

2) In kidney – Tubular involvement

Distal renal tubular acidosis (RTA) [type-1]

Hypokalemia

3) In liver – primary biliary cirrhosis

4) Peripheral neuropathy

- B/L symmetrical small fiber sensory > motor

- lower limb > upper limb polyneuropathy

Look for :

- Persistent parotid enlargement

- Purpura

- Leukopenia

- Cryoglobulinemia

- Low C₄ level

Sjogren leads to marginal zone lymphoma

minor salivary gland [labial] biopsy

→ CD₄ + T cell infiltrate

Anti Ro [m/c] - [SSA]
Anti La - [SSB] } Bad prognosis (extraglandular involvement)

Management

00:12:51

Glandular

Dry eyes - artificial tear drops

Dry mouth - salivary substitutes

Extraglandular:

Arthritis - Hydroxychloroquine

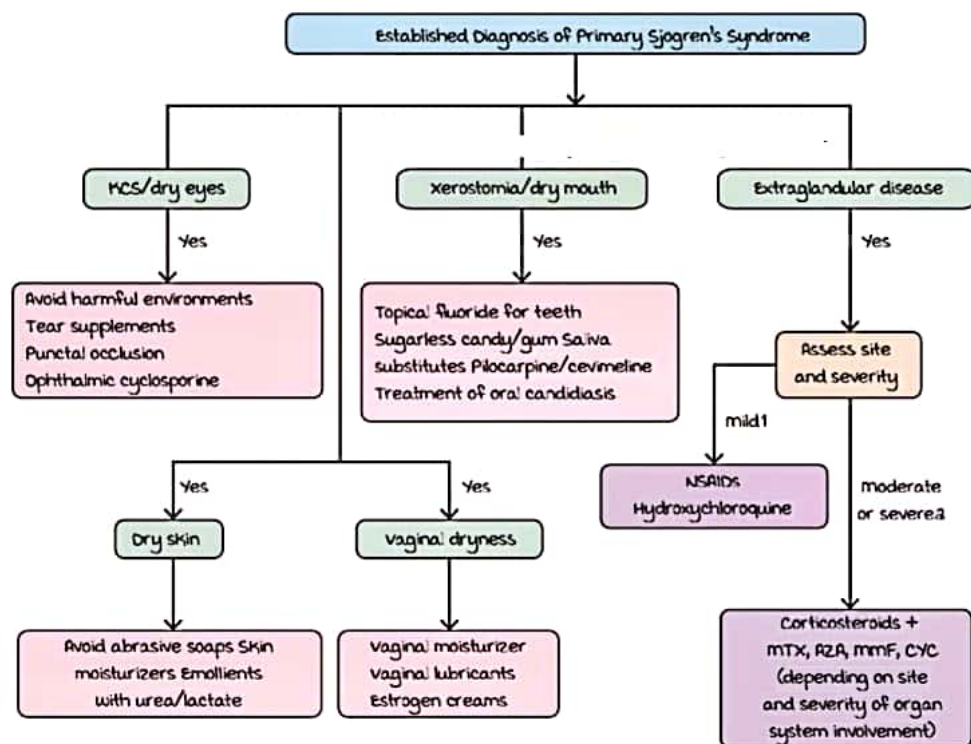
NSAIDS

Lung or other organ system involvement - Oral steroids + methotrexate/
Azathioprine / cyclophosphamide

If patients having ILD - cyclophosphamide

If patients not having ILD - methotrexate or Azathioprine

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.



Active space

- Thickening and induration of skin

Two types:

1. Scleroderma without systemic features
[Localized scleroderma]
- morphea

2. Scleroderma with systemic features [systemic sclerosis]



1. Diffuse cutaneous scleroderma
2. Limited cutaneous scleroderma

[Skin lesions on face and hands/feet]

Pathophysiology:

- Fibrosis of affected organs

+

Small vessel injury [microvascular injury]

- Endothelial injury

[Anti-endothelial antibodies] → vascular remodelling
neo-intimal proliferation



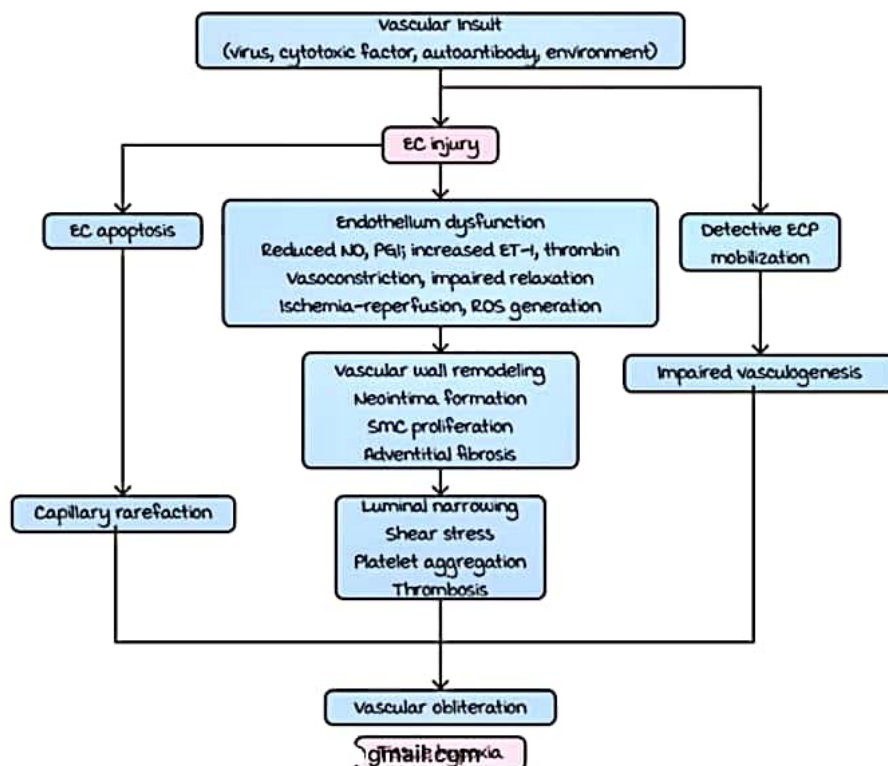
[Non inflammatory fibrotic proliferative obliterative arteriopathy]



[ESR low]

[key pathogenic cytokine - TGF - β]
obliterative arteriopathy (especially in renal vessels) which is a cause for thrombotic microangiopathy (TMA)

Organs: Affected → skin, lungs; GIT; Heart and Kidneys



ROS - Reactive oxygen species

Environmental Agents and Drugs Implicated in
Scleroderma-like Syndromes

Chemicals
Silica
Heavy metals
mercury
Organic chemicals
vinyl chloride
Benzene
Toluene
Trichloroethylene
Drugs
Bleomycin
Pentazocine
Taxol
Cocaine
Dietary supplement/Appetite Suppressants
L-tryptophan (contamination)
mazindol
Fenfluramine
Diethylpropion

- Episodic vasoconstriction in response to cold, stress or vibration
- Pain, numbness and tightness of extremities
- Sometimes associated with severe ischaemia –
Critical limb ischaemia – Gangrene
- Pallor, cyanosis; redness on rewarming

Primary raynauds	Secondary raynauds
[Raynauds disease] - Not associated with CTD - Family history [+] - Young females [20-35] - Less painful; less severe/ No critical limb ischemia - Nail fold capillary microscopy -normal	associated with Scleroderma(m/c) sjogren; MCTD -No family history -middle aged and elderly [40-60 years] -more painful; more severe, critical limb ischaemia Areas - capillary dropout

Diffuse vs limited scleroderma

00:15:33

both present as secondary Raynauds phenomenon

Diffuse scleroderma	limited scleroderma
- Short lasting secondary Raynauds [weeks to months] - No critical limb ischemia	- Long standing secondary Raynauds [months to years] - Critical limb ischaemia - more severe - more painful C calcinosis cutis R Raynaud's E esophagitis S sclerodactyly T Telangiectasia - Anti centromere antibody

Diffuse scleroderma:

- Skin manifestations + short lasting Raynaud's
- Edema / Atrophy and induration



Loss of body oil
Loss of body hair
Extreme
hyperpigmentation



Alternating hypo & hyper
pigmentation
[salt and pepper
appearance]



Extreme fibrosis
Microstomia;
Puckered mouth;
Pursed lip;

"mask facies"



Joint contractures;
Tendon friction rubs;
Arthritis;
Ulcers at the site of
trauma
[friction ulcers]

Critical limb ischaemia:

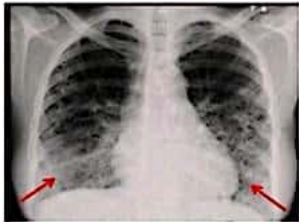
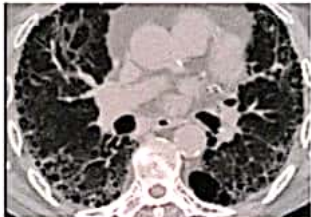


Ischemic
auto
amputation
esoph
acral
osteolysis

Diffuse scleroderma	limited scleroderma
 	

Diffuse scleroderma	Limited scleroderma
Cutaneous Diffuse [more fibrosis] Raynauds short musculoskeletal ✓ Renal ✓ Cardiac ✓ ILD ✓ musculoskeletal: Arthralgia; CTS/tendon friction rub Renal: scleroderma; Renal crisis Cardiac: Restrictive cardiomyopathy pericarditis ILD: Non-specific interstitial pneumonia	Distal to elbow, Face [less fibrosis] Long standing [more severe] Rare GIT is m/c - Lax LES; GERD; Gastric antral vascular ectasia - watermelon stomach intestinal pseudo obstruction; calcinosis cutis Thyroid - involved

Diffuse scleroderma	Limited scleroderma
- Anti - Topoisomerase [Scl-70] antibody - m/c cause of death in scleroderma- Fibrosis [ILD] Few points Systemic sclerosis: F>>m - 5:1 - 30-35 years	Anti centromere Antibody

Lung manifestation:	Limited scleroderma
Asymptomatic sclero-derma-PFT + DLCO Symptomatic scleroderma-HRCT ↓ "Diffuse Type" x-ray - B/L bibasal subpleural reticular infiltrates  usual Interstitial pneumonia (UIP) (or) Idiopathic pulmonary fibrosis Honey comb; Destructive lung architecture; cystic changes; "Traction bronchiectasis" 	- Pulmonary artery hypertension has poor prognosis in limited scleroderma - m/c death → "PAH" When; $\frac{FEV_1}{FVC} - (N)$ ↓ Normal ↓ Restrictive ↓ Vascular [PAH] FVC ↓ Or normal DLCO ↓↓↓



Ground glass
opacification
'NSIP'
[Non-specific
interstitial pneumonia.]

when $\frac{FEV_1}{FVC} = (N)$

Normal

Restrictive
[ILD]

FVC ↓↓↓
DLCO ↓

Vascular
[PAH]

FVC is decreased in ILD

Renal manifestation in scleroderma

Scleroderma renal crisis: Seen only in Diffuse Type

- Within first 4 years
- ACE inhibitors are DOC

Presentation: TMA; micro angiopathic hemolysis; Thrombocytopenia;
Renal failure

Classical schistocytes seen

Anti - topoisomere present

Anti - U3 - RNP present

Antibodies in scleroderma

00:46:10

Topoisomerase I scl-70	Diffuse scleroderma
Centromere	CREST
U3RNP	PAH; ILD; Renal crisis
RNA polymerase III [Fibrillarin]	Diffuse Type Joint contractures; tendon friction rub and renal crisis
Anti Ku	SLE and scleroderma overlap

Management of scleroderma

00: 49: 48

- ANA 95%
- Anti SCL - 70 50%
- Anticentromere 75%

No single drug found to be useful

Steroid plus cyclophosphamide → ILD

Nifedipine / Anticoagulation / Bosentan → PAH

ACE inhibitors → Renal crisis

In trial: Pirfenidone - Anti TGF beta

d - penicillamine - Anti fibrotics

drugs used in Raynauds phenomenon:

DOC- Bosentan

Ca⁺ channel blocker → Nifedipine; Prostacyclin(Iloprost -parentral);

α - blocker -prazosin; ARB - Losartan;

PDE inhibitor: Sildenafil

Surgery: sympathectomy

INFLAMMATORY MUSCLE DISORDERS

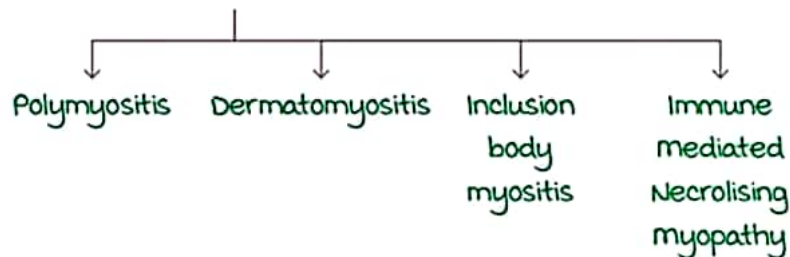
INTRODUCTION

00:00:08

- Also called idiopathic inflammatory myositis
- Systemic sub acute autoimmune inflammation with mononuclear cell infiltrate in muscle



Persistent muscle weakness



Polymyositis vs Dermatomyositis

00:02:06

Polymyositis	Dermatomyositis
- Only in Adults - Age: 40 yrs - Never manifests alone - Skin feature ⊖ - F >> m	- Adults & Children (In children Juvenile dermatomyositis) - Can present alone or with other autoimmune condition - Skin features ⊕ occur before / concurrently or after muscle involvement - F >> m

Clinical presentation

00:03:59

Bilateral Progressive Symmetrical subacute presentation

Proximal LMN weakness

LL > UL

mild myalgia ⊕

Difficulty in climbing stairs

Difficulty in getting up

Active space

Difficulty in standing up from squatting position

Involvement at each level presents as:

Anterior horn cell: → Asymmetric, fasciculations ⊕, atrophy

Radical → Pain along distribution, asymmetric

Nerve → Sensory Involvement ⊕
Distal to proximal involvement

NMJ → myasthenia like presentation

muscle → Tendon reflex preserved,
Sensory - Normal

Intermittent

Persistent

- ↓
- 1) Poly / Dermatomyositis
 - 2) Hypothyroid myopathy
 - 3) Drug induced myopathy

Subacute progressive symmetrical proximal (LL > UL) weakness

→ DD: Dermatomyositis / Polymyositis

Peculiarities are:

- a) pharyngeal & neck flexor involvement
- b) Extra ocular & facial muscle always spared
- c) Respiratory muscle, involved very late

Screening: ↑↑↑ CK

IOC : muscle biopsy

Dermatological manifestation of dermatomyositis

00:09:05

- Only in dermatomyositis

1) Gottron's papule: They are pathognomic

Violaceous, flat topped papule on extensor aspect on MCP & PIP Joint

2) Gottron Rash / Sign:

3) Heliotrope Rash: Violaceous periorbital edema / erythema

4) V sign on anterior neck

5) "Shawl sign" on posterior neck

6) Periungual erythema and Nailfold telangiectasia

- 7) Calcinosis cutis
- 8) Linear erythema of finger
- 9) Holster sign - "Poikiloderma lesion on lateral aspect of thigh"

Antibodies associated with poly / dermatomyositis 00:13:55

1. Anti Jo/Synthetase antibody

Polymyositis > Dermatomyositis

causes:

- 1) Arthritis (similar to SLE)
- 2) Interstitial lung disease (NSIP)
- 3) Raynaud's phenomenon (2°)
- 4) mechanic hand

Crusting of lateral aspect of index & middle finger (Seen in both polymyositis / Dermatomyositis)

2. Anti SRP (Signal Recognition peptide)

Polymyositis >>> Dermatomyositis,
denotes Cardiac involvement

3. Anti helicase (mia) antibody

Only seen in dermatomyositis

Diagnostic Features	Dermatomyositis	Polymyositis	Inclusion Body myositis
Clinical features			
Age	Children and adults	Adults	Adults >50 yr
Disease onset	Subacute	Subacute	Chronic
Muscle weakness	Proximal	Proximal	Selective pattern
Symmetry	Symmetric	Symmetric	Asymmetric
Systemic features	Yes	Yes	Yes
Skin changes	Yes	No	No
Calcinosis	Yes	Rarely	No
Associated connective tissue disease	Yes	Yes	Yes

Associated malignancy	Yes	Yes	Yes
Laboratory features			
Serum enzymes	Normal to high	Normal to high	Normal to high
Abnormal EMG	Yes	Yes	Yes
Abnormal muscle biopsy	Perifascicular atrophy, capillary depletion, patchy MHC class I expression and microinfarcts	CD 8 T cell invasion of non necrotic fibers and MHC class I expression on fibers	CD 8 T cell invasion, MHC expression vacuolated fibers, and tubulofilamentous inclusions in fibers

Both polymyositis/ Dermatomyositis can be Paraneoplastic

Ca Ovary - most striking

Also Adenocarcinoma of stomach & Lungs

muscle biopsy:

Dermatomyositis

Perifascicular atrophy

Polymyositis

CD 8 + T Cell invasion

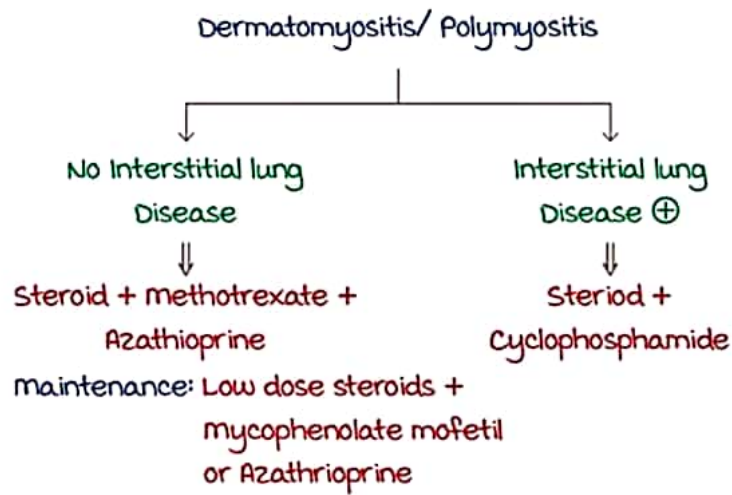
Inclusion body myositis

00:18:40

- Chronic
- m > F (Age 50 Yrs)
- Distal asymmetrical
- Quadriceps involvement ⊕
⇒ "recurrent falls"
- Paraneoplastic
- No skin changes

Management

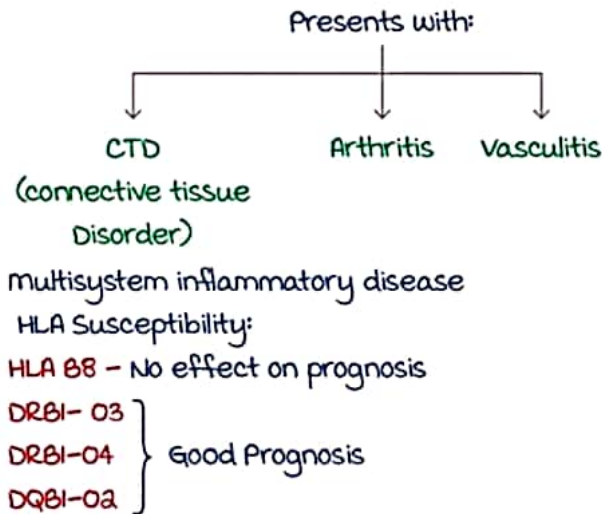
00:19:34



SARCOIDOSIS

Introduction

00:00:08



$\frac{2}{3}^{\text{rd}}$ (50-70%) → spontaneous Resolution

20% → Chronicity



5% → Death (due to Interstitial Lung Disease)

- CD_4 + T Cell mediated inflammation, characterised by Non-caseating granuloma
- Immune Paradox:
 - Enough CD_4 + T cell → infection +
- Other causes of Non caseating granuloma:
 - a) Berylliosis
 - b) Crohn's disease
 - c) HSP (Hypersensitivity Pneumonitis)
 - d) Cat scratch disease

Organs involved in sarcoidosis

00:04:06

- Any age (F > m)
- Can involve any organ

Active space

D) Skin:

Acute: (Good prognosis)

Lofgren syndrome	Heerfordt Waldenstrom
• B/L Hilar adenopathy • Arthritis • Erythema Nodosum (+ uveitis in 5%)	- Waldenstrom - Uveitis - Parotitis - A/I. I. MN I 7th nerve palsy

Chronic: Lupus Pernio (Bad Prognosis)

Crusted erythematous maculopapular

Lesion on face or violaceous papule

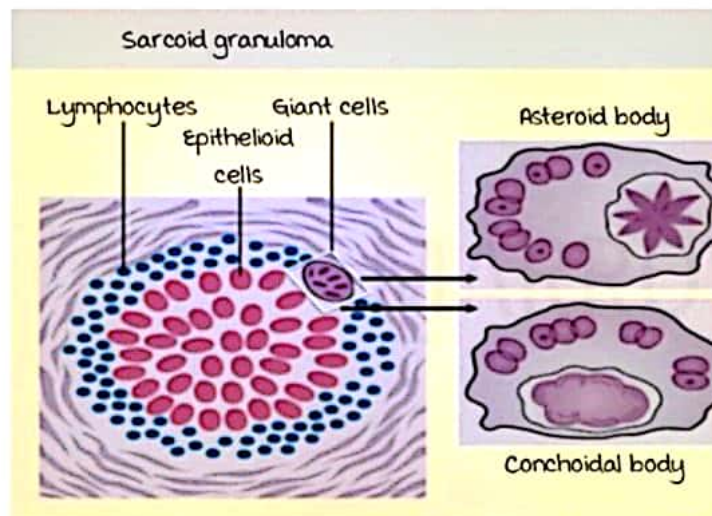
On nose / face with dilated capillaries



Sarcoid granuloma:

1) Asteroid body

2) Conchoidal body



2) Eyes:

- Chronic anterior uveitis (m/c) > Acute anterior uveitis
- Posterior uveitis > Retinitis

3) Lungs (m/c organ involved)

- Fever, myalgia, weight loss, Non-specific cough

↓
x-ray
↓

Hilar lymphadenopathy

↓

Biopsy: Non caseating granuloma

Staging based on chest-xray finding

00:09:12

Scadding scoring System:

Stage 1: B/L Hilar Adenopathy

Stage 2: B/L Hilar Adenopathy + Infiltrates

Stage 3: Infiltrates alone

↓

Ground glass opacification
(Non specific interstitial pneumonia)

↓

Involve upper lobe (only connective
tissue disorder involving upper lobe)

Stage 4: Fibrosis

In Rheumatology, only 3 things involve upper lobe of lungs:

- 1) Ankylosing spondylitis
- 2) Sarcoidosis
- 3) Psoriatic Lung disease

Other conditions involving upper lobe:

- 1) Berylliosis
- 2) Radiation induced Lung disease
- 3) Hypersensitivity pneumonitis
- 4) Langerhans cell histiocytosis

Garland Sign: Right + Left Hilar Lymphadenopathy + Right
paratracheal Adenopathy

4) Cardiac

Conduction defects

Restrictive cardiomyopathy > Dilated cardiomyopathy

5) Hepatic

Intrahepatic cholestasis

6) Renal

- Chronic Tubulointerstitial disease

- m/c Glomerular disease: membranous nephropathy

7) Haematology

- Lymphadenopathy

- Splenomegaly due to hypersplenism

8) Metabolic

- Hypercalcemia (due to production of 1,25 (OH)₂ cholecalciferol)

9) Neuro:

B/L LMN 7th Nerve Palsy

- ↳ DD:
1. Sarcoidosis
 2. Guillain Barre syndrome
 3. Diphtheria
 4. Lyme disease

Pituitary stalk involvement

- Central Diabetes Insipidus

Transverse Myelitis

Hypothalamic involvement

Basilar meningitis

Diagnosis

00:16:00

Old method: Ga - 67 Scan

↳ Panda sign / Lambda sign (outdated)

Now a days: IOC: PET Scan biopsy

ACE levels normal can rule out sarcoidosis

ACE high: DD: 1. Gaucher's disease

2. Miliary TB

3. Leprosy

4. Hyperthyroidism

In BAL $\frac{CD_4}{CD_8}$ ratio is high ($\uparrow\uparrow$) in sarcoidosis

If $\frac{CD_8}{CD_4} \uparrow\uparrow \rightarrow$ Hypersensitivity Pneumonitis

Rare findings:

- Only in Indian Patients
 - multiple Red papules over cheek & chin
- Osteolysis
 - Perthes Jungling disease

Paradoxical response

00:18:04

1) Immune paradox

2) Clinical paradox

- As lung disease worsens, Nodal enlargement usually regresses
- Can present with Anaemia & splenomegaly
- Drug related Sarcoid like lesions : Anti TNF α therapy
- markers:
 - 1) ACE
 - 2) Serum Amyloid A
 - 3) Soluble IL 2 receptor

Treatment:

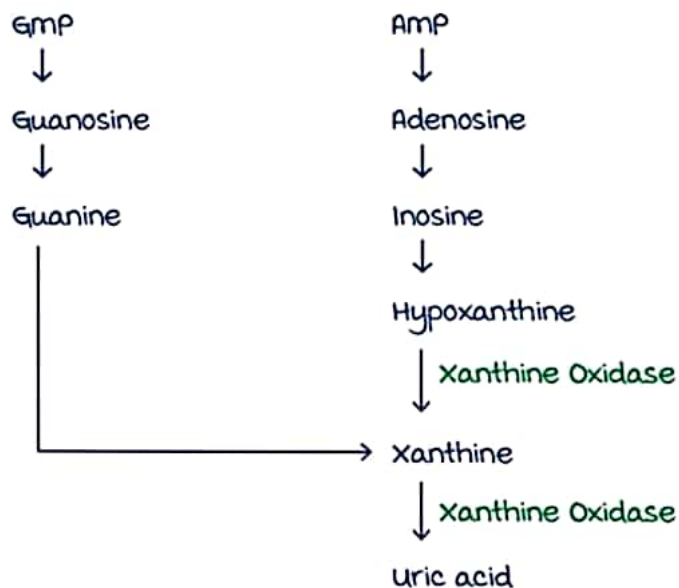
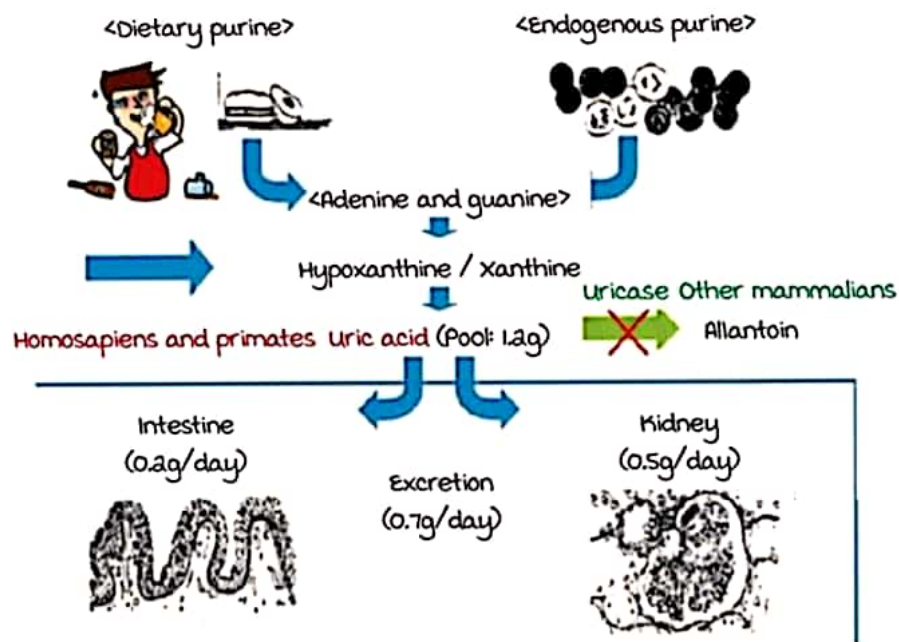
Acute: No drugs required

Optional - steroids

Chronic: Steroids + methotrexate or Azathioprine

2nd line: Anti TNF- α

CRYSTAL ARTHROPATHY



uric acid → Breakdown product of purine metabolism

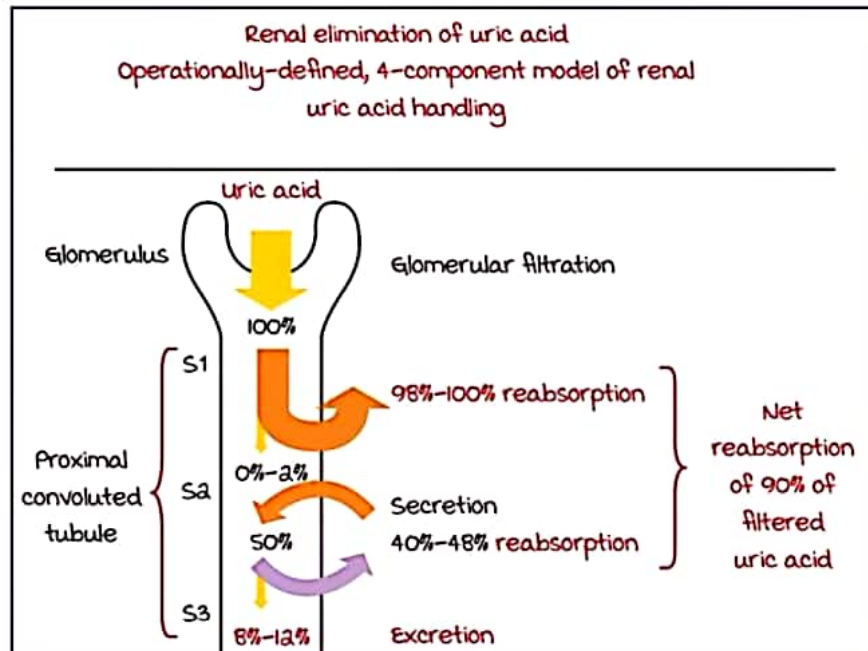
uric acid pool - 1.2 g/day

Daily Excretion ~ 700mg/day

urine Excretion ~ 500mg/day

24 hr urine uric acid = 11 mg/kg/day

4 Component handling of uric acid (handled by kidney) 00:03:29



100% filtered

100% reabsorbed at S₁ of PCT

50% Secreted at S₂ of PCT

40% reabsorbed at S₃ of PCT

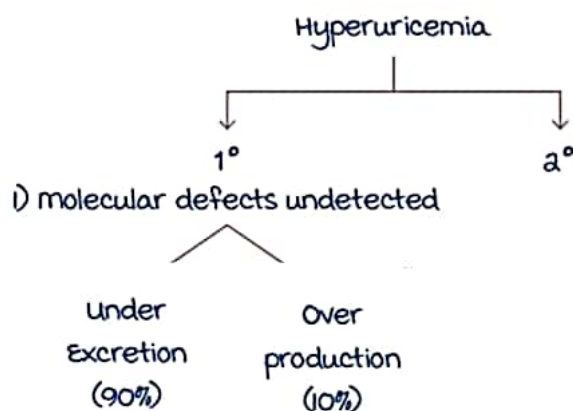


Net Result = 10% Excreted

(100/50/40 rule)

Classification of hyperuricemia

00:05:06



a) Associated with specific enzyme defect

- x linked
- ↑PRPP synthetase

Secondary hyperuricemia:

a) ↑ uric acid synthesis denovo (Purine bio-synthesis)

1) HGPRTase defect:

- Lesch Nyhan Syndrome

(mental Retardation, Hyperuricemia, Self mutilation)

2) ↓ Glucose - 6 - Phosphatase

- Von Gierke's disease

Hypoglycemia, Lactic acidosis, Hyperuricemia, Hyperlipidemia,
Doll facies, Seizures

3) Fructose - 1 - Phosphate aldolase defect

b) Idiopathic

c) Drugs

1) Thiazides

2) Pyrazinamide

3) Nicotinic acid

4) Salicylate

5) Alcohol

6) Cyclosporine

7) Loop diuretics

8) Ethambutol

d) ↑ ATP degeneration

Losartan → Increased uric acid excretion

preferred in HTN with hyperuricemia

Clinical presentation

00:10:54

Hyperuricemia (> 6.8mg/dl - male

> 6mg/dl - Female)

can be : asymptomatic or affect joints(gouty arthritis) or present
with renal manifestations

Asymptomatic hyperuricemia :

- Considered as a part of Insulin resistance and is included in metabolic syndrome
- Correlate directly with Sugars / Cholesterol / Creatinine / BP
- ↑ risk for developing gout (first attack after 20 yrs)
- Alcohol / Sea food / Red meat - ↑ uric acid level

Renal disease due to uric acid

00:15:30

I Uric acid Nephropathy

- Tumour lysis syndrome

II Urate Nephropathy

- Chronic long standing hyperuricemia related tubulo-interstitial damage

Other causes:

1) Hyper Oxaluria

2) ↑ uric acid

3) Hyper Ca^{2+}

4) Hypo Kalemia

Can lead to chronic long standing hyperuricemia related tubulointerstitial damage

Lead Poisoning: ↑ uric acid CTID

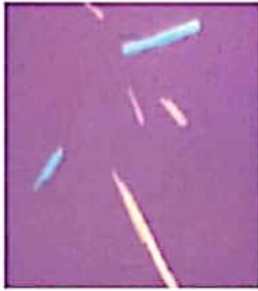
Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Joint manifestation

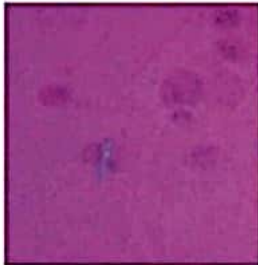
00:18:09

I) Acute Gouty Arthritis

- Fluctuations in the level of uric acid triggers it
- Alcohol & Sudden lowering of uric acid by drugs triggers it
- M>F (40-60yr)
- Asymmetrical onset
- Clinically - MTP of great toe affected
- Rarely ankle/ wrist / knee
- acute on chronic presentation maybe seen
- Explosive onset (Extreme pain)
- Hot red dusky swollen joint & Signs of inflammation
- X-ray ⇒ ↑ Soft tissue density
- Polarised light microscopy
 - Negatively bi-refringent needle shaped Crystals containing msum (monosodium urate monohydrate)

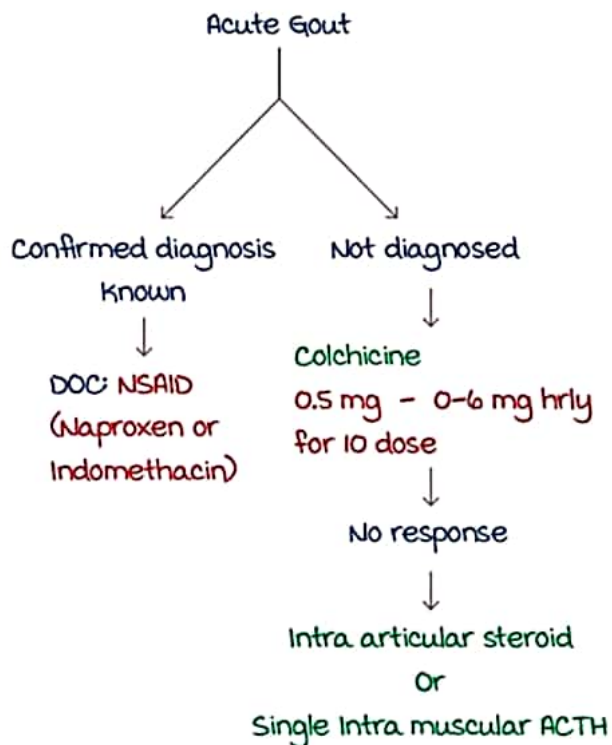


Polarized light microscopy of urate crystals. Illustrated are extracellular birefringent needle-shaped urate crystals



Polarized light microscopy of urate crystals. Illustrated are intracellular birefringent needle-shaped urate crystals

Treatment



New drugs:

- IL-1 β antagonist
 - Anakinra / Canakinumab / Rilonacept

Chronic tophaceous gout

00:24:41

- "Tophi" - marker of chronic gout
- Irregular asymmetric moderately discrete tumescence that we see on hands / Feet / Olecranon / Forearm / Antihelix of ear

- Painless
↓
Acute inflammation around tophi makes it painful

1st episode of acute gout

↓ 12 yrs

Chronic gout

Rate of tophus formation correlates with degree and duration of hyperuricemia

X-ray finding of chronic tophaceous gout

- Asymmetrical
- Punched out erosion
- Lytic lesions
- Overhanging edges
- Sclerotic borders
- Differ from rheumatoid arthritis
 - maintenance of the joint space
 - Absence of periarticular
- Osteopenia
 - Location outside the joint capsule



RA Vs Chronic tophaceous gout

In chronic gout: maintenance of joint space, absence of peri-articular osteopenia

“martell Sign or G sign” - Overhanging edges

Treatment:

Chronic tophaceous gout (on asymmetric hyperuricemia)

Aim: To control hyperuricemia

I Drugs which inhibit xanthine Oxidase

- Allopurinol
- Oxypurinol
- Febuxostat

II Uricosuric drugs

- Probenecid (Sulfinpyrazone)
- Benzbromarone (Lesinurad)

III Recombinant Uricase

(Specifically used for tumor lysis syndrome)

- Rasburicase
- Pegloticase

(Infusion reaction can occur and are dangerous)

Xanthine oxidase

00:31:01

1) Allopurinol

- No role in acute gout
- Sudden lowering with drug can trigger attack

HLA B*57:01, B*58:01 → Sudden hypersensitivity to drug (SJS)

S/E: GI Intolerance, Bone marrow Suppression, Alopecia, Hepatitis

↑ T_{1/2} of warfarin, Theophylline

Starting dose: 300mg / day (if renal failure: 100mg / day)

2) Febuxostat

- Safe in Renal failure
- Less side effects

Uricosuric drugs

00:33:35

Severe Gastrointestinal distress

Hypersensitivity ⊕

↓ Renal excretion of penicillin / Salicylate

Benzbromarone is safe in renal failure

Food grouping acc. To purine content

- Group: 1 high purine content
(100 TO 1000mg of purine nitrogen per 100gms of food)

Anchovies	mackerel
Bouillon	meat extracts
Brains	mince meat
Broth	mussels
Consomme	Partridge
Goose	Roe
Gravy	Sardines

Food in this list should be omitted from the diet of patients who have gout (acute and remission stages)

Associations of hyperuricemia:

- 1) Atherosclerosis
- 2) Type 2 DM
- 3) Systemic hypertension
- 4) Hyper triglyceridemia
- 5) Hypothyroidism

Pseudogout

00:35:36

- Seen in elderly males (65 - 75 yrs)
- due to calcium pyrophosphate deposition
- Painless
- mostly involve knee joint
- Non inflammatory arthritis
- ANKH gene mutation ⊕
- Wrist / Shoulder may be involved
- X-ray ⇒ Chondrocalcinosis ⊕
- Positively birefringent Rhomboid crystals prove diagnosis
- Always do synovial study
- Fever ⊕
- Rx: NSAIDs / Steroids
- associated with:
 - 1) 1° hyperparathyroidism
 - 2) Hemochromatosis
 - 3) Hypophosphatasia
 - 4) Hypomagnesemia (Gitelman syndrome)

Calcium apatite deposition disease

00:39:32

- In areas of tissue damage / CKD / hypercalcemia
- Shoulder joint involvement
 - ↳ Milwaukee shoulder
- mostly asymptomatic or can cause destruction

- Intra articular calcification ⊕
- Non - inflammatory (Synovial fluid WBC count - low)

Calcium oxalate deposition disease

00:40:54

Envelope shaped - Ca Oxalate dihydrate

Dumbbell shaped - Ca Oxalate monohydrate

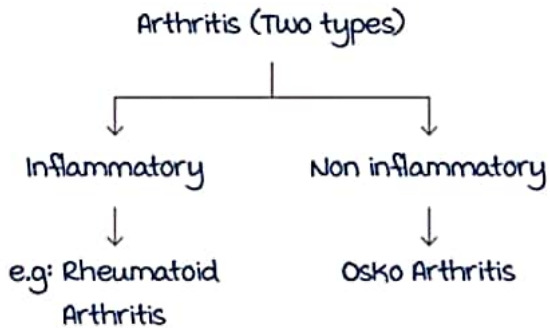
Positive birefringence crystals

Non - Inflammatory

Involves bone / Articular cartilage

m/c : Finger, wrist, elbow

INTRODUCTION TO INFLAMMATORY ARTHRITIS



Diagnostic approach :

1) Arthralgia or Arthritis

Arthralgia



Pain around joint

Arthritis



Inflammation (redness, warmth)

or

Pain

or

Tenderness

or

Edema

2) Inflammatory or Non-inflammatory

a) History

morning stiffness

- All inflammatory arthritis → morning stiffness is relieved by activity & exacerbated by rest

- Duration:

Peripheral arthropathy > 45 min

Axial arthropathy > 30 min

b) Clinical finding



Features of inflammation at joint

c) Lab markers:

ESR, CRP

Serum ferritin, platelet count

Active space

d) X-rays:

Rarefaction or erosion of inflammatory arthritis

e) Best Test

Synovial fluid WBC count > 5000/ml

3) unilateral or bilateral

4) Involving - lower limb

Or

Upper limb

Or

Combined

5) mono arthritis

Or

Oligoarthritis

Or

Polyarthritis

6) Involving small joints

or

Large joints

or

Combined

• In case of Rheumatoid Arthritis

1) Arthritis

2) Inflammatory

3) Bilaterally Symmetrical

4) Predominantly upper limb

5) Small joint

6) Polyarthritis

} Same features can be seen in Sjogren's syndrome & SLE

Additional findings in RA :

1) On X-ray

↓

If erosions present → Rheumatoid Arthritis

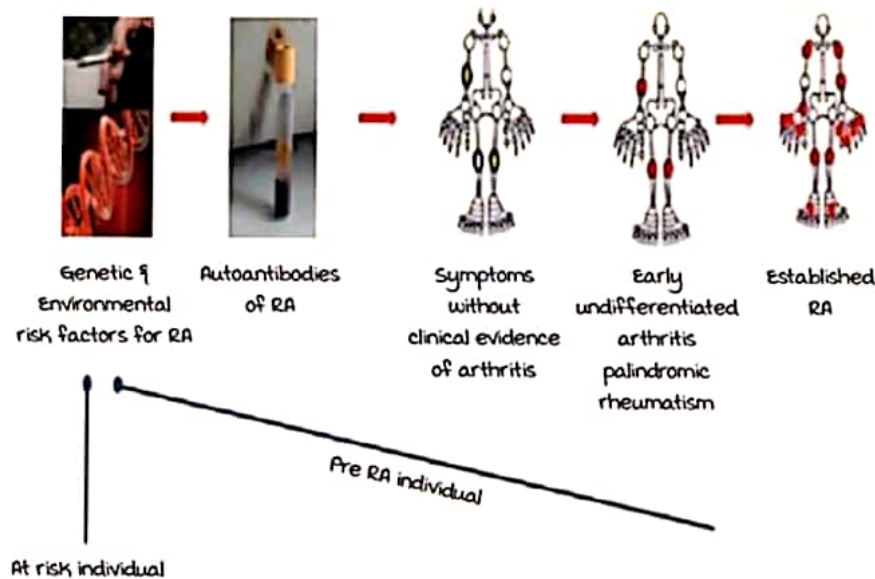
2) markers

- Anti-CCP (Anti-Cyclic citrullinated peptide)
- Rheumatoid factor (RF)

Rheumatoid arthritis (RA)

00:12:18

- most common chronic inflammatory, symmetrical involving small joint (upper limb) Peripheral **erosive polyarthritis**
- Risk of Rheumatoid Arthritis $\uparrow > 40$ yrs Age
- $F > m$, F : m ratio 3 : 1



Pre - RA

00:15:50

- 1) genetic and environmental susceptibility
- 2) Antibodies positive for RA
- 3) Clinical evidence without the evidence of arthritis
- 4) Early undifferentiated arthritis also known as **palindromic rheumatism**

1) genetic and environmental susceptibility:

- Genetic:
 - Females > males
 - **HLA DRB1 04** - Causative
 - HLA DRB1 01, 03, 05, 07 } Certain alleles are protective
- **15%** concordance in identical twins

- Environmental risk factors
 - Strongest risk factor → **Smoking**
 - No single causative infectious agent is established
 - **Chronic periodontitis** is also risk factor

a) Auto antibodies

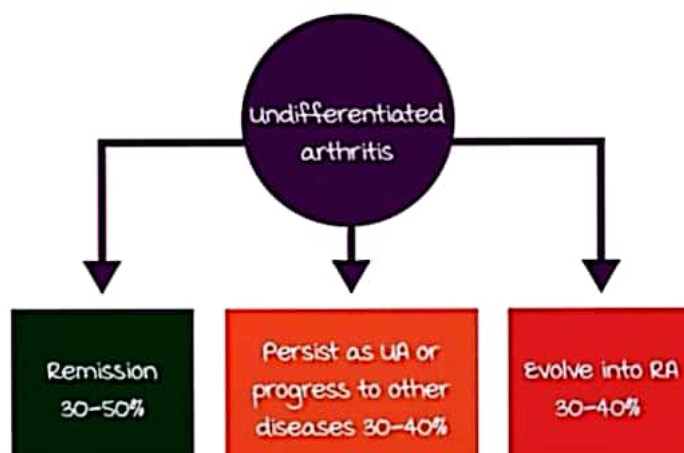
For eg: A 50 year old female complains of

Pain in small joints in both upper limb right side > left side with early **morning stiffness** relieved with activity

On examination → Normal

Differential diagnosis : **Undifferentiated Arthritis**

- Evaluate : **ESR and CRP**



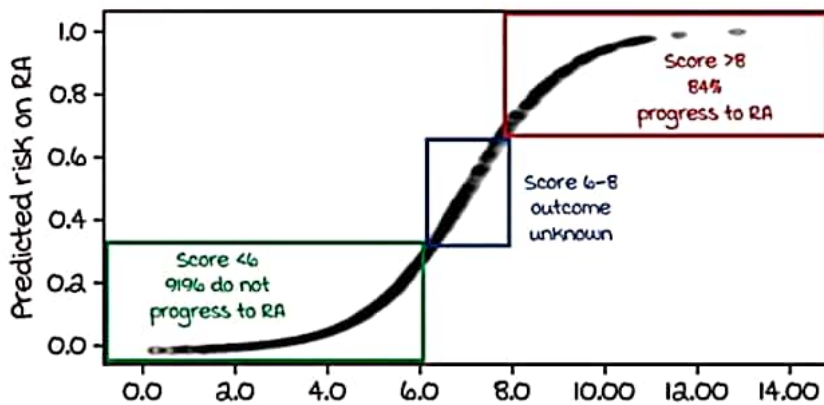
- $\frac{1}{3}^{\text{rd}}$ of patients with **undifferentiated arthritis** can progress into **Rheumatoid Arthritis**

Risk factor score for RA

00:24:52

Variables		Score
Age (years)		X0.02
Female		1
Joint distribution	Small joints of hand / Feet	0.5
	Symmetry	0.5
	upper limb	1.0
	upper & lower limb	1.5

Variables		Score
morning stiffness (on 100mm VAS)	26-90mm	1.0
	>90mm	2.0
Tender joints (n)	4-10	0.5
	>10	1.0
Swollen joints	4-10	0.5
	>10	1.0
CRP (mg/L)	5-50	0.5
	>50	1.5
RF positivity		1
ACPA positivity		2



Serology

00:25:10

- In early undifferentiated Arthritis
 - 1) CRP +ve
 - 2) Anti-CCP +ve
 - 3) RF +ve
 } ↑ risk for development of RA
- 2 out of 3 Positive → high risk of progression to RA

Rheumatoid Factor (RF) :

- IgM Antibody → Against Fc portion of IgG
- Seen in 75-80% cases of RA
- increased risk for progression from undifferentiated Arthritis
- increased risk for articular complications in RA
- 'no role in follow up'

Anti-CCP

- CCP → Cyclical citrullinated polypeptide
Or
mutated citrullinated vimentin (anti-mCV)
- Anti - CCP Antibody is seen in 85-90% of RA cases
- more specific than Rheumatoid factor (RF)
- ↑ risk for extraarticular features
- ↑ risk for progression from undifferentiated arthritis

From established RA $\xrightarrow{\text{after 2 years}}$ Progress to chronic stabilized RA

- Pre - RA → 1st 3 months duration
- Established RA → 3-24 months
- Chronic stabilized RA → After 24 months

Indian Rheumatology Association - Classification of RA:

- VERA - Very Early Rheumatoid Arthritis → Within 1st 3 months
- Early established RA → Within 1 year
- Late established RA → 1-2 years
- chronic stabilised RA > 2 yrs

Pathogenesis

00:34:04

- Inflammation - Arthritis
Tendinitis
Bursitis
- inflammation starts at 'DRUJ' (Distal Radio Ulnar Junction)
- Tcell + B cell mediated
- Key pathogenic cytokine in RA → TNF- α
- Osteoclasts are activated



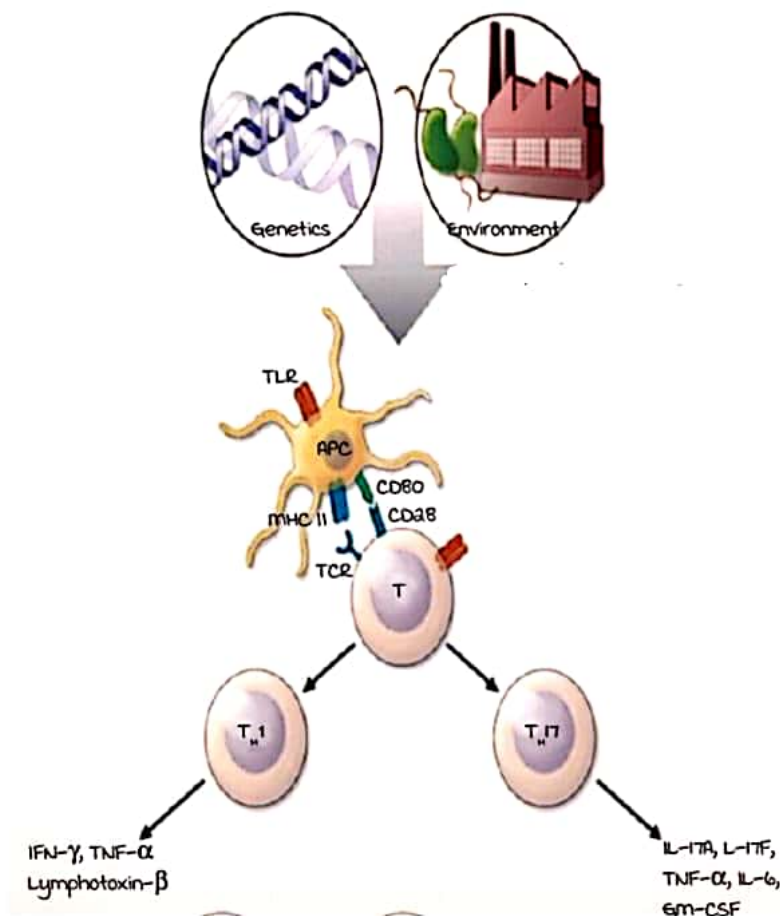
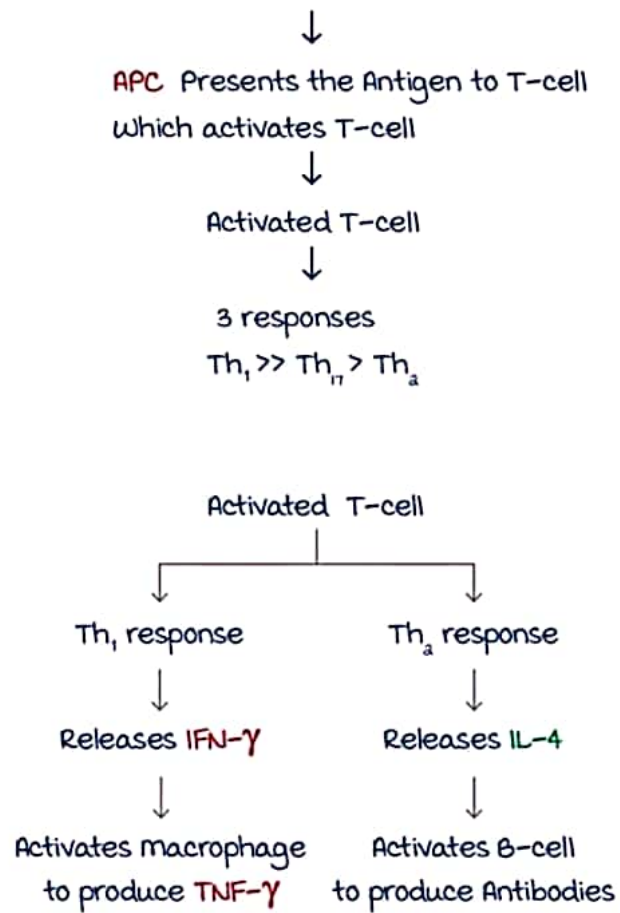
Bone resorption

Genetic + Environmental factors

Activates

Antigen Presenting cells (APC)





TNF- α

- TNF- α inhibits osteoblasts by DKK-1 pathway also known as Dickkopf pathway
- Activates osteoclast - By RANK-L/RANK interaction
- RANK receptor present on the Inactive Osteoclast
- osteopontogenin prevents binding of RANK-L to RANK Receptor
- In Rheumatoid Arthritis

TNF- α Blocks Osteoprotogerin



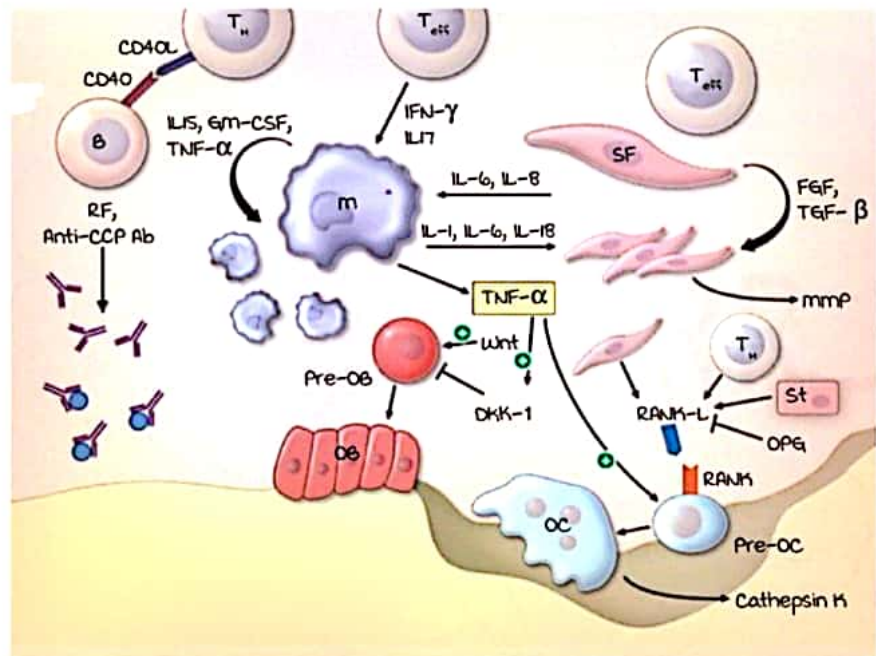
Releases RANK-L from Activated macrophage



Facilitates RANK-L-RANK interaction



Activates osteoclast



RHEUMATOID ARTHRITIS – ARTICULAR & EXTRA ARTICULAR MANIFESTATIONS

- It's an inflammatory arthritis starting at the **Distal Radio Ulnar joint (DRUJ)**
- main inflammatory cytokine
 - ↓
 - TNF - α - which is released from activated macrophage
 - As a part of **Th₁ response**
- Three joints are involved at the same time
 - Wrist joint
 - metacarpophalangeal (MCP) joint
 - Proximal interphalangeal (PIP) joint
- Distal interphalangeal joint (DIP) is not involved in **Rheumatoid arthritis**

Pathology

00:02:12

Inflammation of synovium

↓ results in

Synovial Hypertrophy

- Inflammatory granulation tissue that causes hypertrophy of joint space is called **pannus**
- Changes in joint due to synovial hypertrophy

1) **Zig-Zag Deformity:**

- It's not a true deformity
- **Earliest change** in Rheumatoid Arthritis
- Radial deviation at the wrist joint
- Ulnar deviation at metacarpophalangeal (MCP) joint



a) Piano key deformity of the ulnar styloid:

- This is also not a true deformity
- It is due to rupture of Extensor Carpi ulnaris Tendon

3) Subluxation of metacarpophalangeal (MCP) joint:

Due to Synovial Hypertrophy



There is subluxation of MCP joint



Synovitis of metacarpophalangeal joint
with volar subluxation of digits



Synovitis of
metacarpophalangeal
joint

True deformities in rheumatoid arthritis

00:06:33

As the disease progresses, true deformities occur

1) Buttonhole or Boutonniere deformity:

- Flexion of PIP (proximal interphalangeal) joint
- **Hyperextended** DIP (Distal Interphalangeal) joint
- This is due to
synovitis of PIP joint and subluxation of lateral band

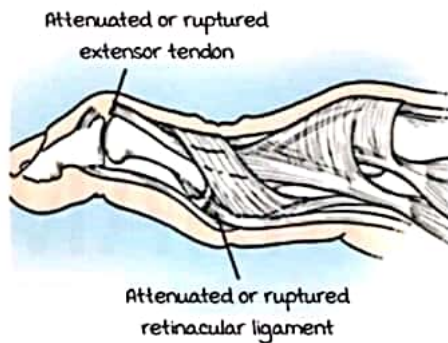


a) Swan neck deformity:

- Hyperextended PIP (proximal interphalangeal) joint
- **Flexion** of DIP (Distal interphalangeal) joint



- Swan neck deformity is due to **rupture** of flexor digitorum superficialis tendon



So, no flexion of PIP joint
PIP joint goes into **Hyperextension**
And **secondary flexion** of DIP joint

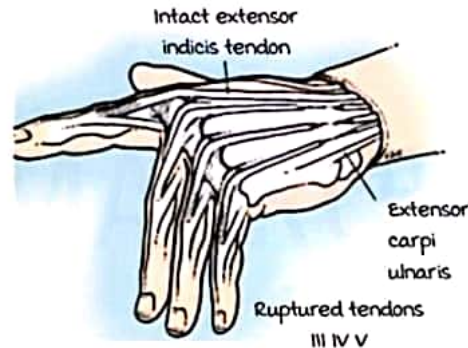
3) Hitchhiker thumb deformity:

- Abduction of thumb
- Hyperextension of Interphalangeal joint of thumb
- This is known as **Hitchhiker thumb deformity**

4) Vaughan Jackson syndrome: (deformity)

- Due to rupture of **extensor tendons** of III, IV, V

Only extensor indices tendon is intact



5) Intrinsic plus deformity:

- Due to chronic tightness of **Intrinsic muscles**



Causes subluxation of MCP joint resulting in

Flexion of MCP joint

Extension of

interphalangeal joint



Causing intrinsic plus deformity



6) Opera glass hand deformity:

- It's an arthritis mutilans of hand
- Shortening of fingers

Due to destruction of
phalanges



Excessive skin gets folded
transversely resembling
'opera_glass'.



DIP deformities in Rheumatoid Arthritis

- DIP joint arthritis is not seen in Rheumatoid Arthritis

DIP deformities in RA

00:15:16

mallet finger

- Hyperflexion of DIP joint
- Which can be seen in
 - 1) Swan neck deformity
 - 2) loss of central slip of extensor tendon



- DIP deformity in Rheumatoid arthritis is mallet finger

Gamekeeper's Thumb/skier's Thumb:

- Ulnar collateral ligaments of MCP joints are destroyed due to synovitis



Resulting in laxity of
the ulnar collateral
ligament of MCP joint

Game Keeper's thumb



Torn ulnar
collateral
ligament

Lower limb in rheumatoid arthritis(RA)

00:20:30

- In lower limb, first joint to be affected



metatarsophalangeal(MTP) joint

Classical deformities

Pes planus
Forefoot Varus
Ankle valgus
Or
Triad

Cock up toe deformity



Cock up toe deformity

Hallux valgus
+
Hyperflexed digits

- Rarely knee joint may be involved

3 Striking joints involved in Rheumatoid Arthritis

1) Temporomandibular joint

2) $C_1 - C_2 \rightarrow$ Atlanto - Axial joint

The axial joints are not involved in Rheumatoid Arthritis except $C_1 - C_2$

3) Crico - Arytenoid Arthritis

Extra- articular manifestations of RA

00:24:38

- most common cause of death in RA



MI



Due to Accelerated atherosclerosis

- So, RA is also known as MI equivalent

1) Neuro -ocular

- RA doesn't involve brain parenchyma so, cognitive dysfunction is extremely rare

- $C_1 - C_2$ Atlanto - Axial joint involvement



Cervical myopathy

- Entrapment neuropathy



Due to synovial hypertrophy resulting in
Compression of nerve
Carpal Tunnel syndrome

- most common ocular manifestation is Dry eye

- most common cause of secondary Sjögren's syndrome

Episcleritis → Acute painful red eye

Scleritis

↳ most characteristic manifestation associated with long term RA

Can lead to visual loss

- Uveitis is not seen in RA

a) Cutaneous manifestation:

- RA nodule or Rheumatoid node



Painless nodule

- Occurs mostly on pressure areas:
Elbow (most common)
Finger
Olecranon

- Associated with ↑ RF Titres
↓
Bad prognosis



Rheumatoid nodules in olecranon bursa and along proximal ulna.

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

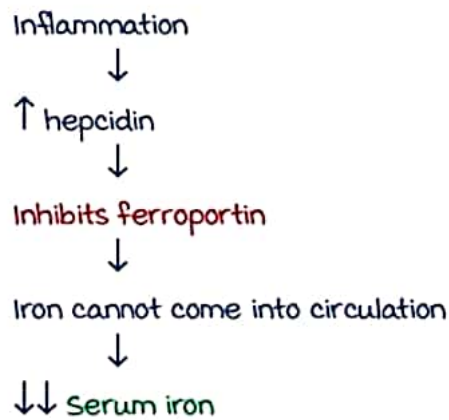
- It is also associated with more extraarticular features
- Only 10% of RA cases develops nodules in the 1st year
- It's a late manifestation

- Palpable purpura
Petechiae
Vesicles
Bulla
Ulcers (rare)
- } Small vessel vasculitis

- Erythema nodosum
 - Pyoderma Gangrenosum
- } very rare

3) Hematological manifestation:

- Anaemia of chronic disease (most common)



- most sensitive & specific indicator is ↓↓ Serum iron
- Warm antibody (IgG) AutoImmune hemolytic anaemia

↓
Coombs Test +ve

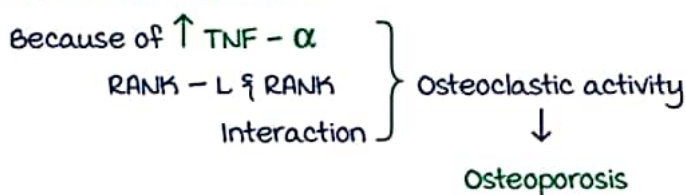
- In late stages of RA
RA + Neutropenia + Splenomegaly
Felty's syndrome (very rare)
- Felty's syndrome has to be always differentiated from Leukemia & Lymphoma
- Large Granular Lymphocytic Leukemia (LGL) can behave very similar to Felty's syndrome
- So, Felty's Syndrome is a diagnosis of exclusion
- RA is a premalignant condition → ↑ ed risk of DLBCL
(Diffuse large B-cell lymphoma)

4) Cardiac manifestation

- Pericarditis without Tamponade – most common
- Endocarditis is very rare
- most common valvular lesion → Mitral Regurgitation
- most common Arrhythmia → Ventricular Tachycardia

5) Endocrine manifestation: → Hypoandrogenism

6) Skeletal manifestation:



7) Renal manifestation:

- most common association of RA



Secondary membranous nephropathy

- Long standing RA produces 2° Amyloidosis



AA Amyloidosis

8) Gastrointestinal manifestation:

GI vasculitis



mesenteric artery vasculitis (medium vessel vasculitis)



mesenteric ischemia

Lung involvement

00:39:08

- most common lung manifestation



Pleuritis ± effusion

- Pleural effusion in RA

- Lymphocytic exudative effusion
- unilateral >> Bilateral
- ↑ Protein
- ↑ LDH
- Low pleural fluid glucose (<30g/L) – diagnostic of RA

- High LDH also seen in Empyema



To differentiate it from RA

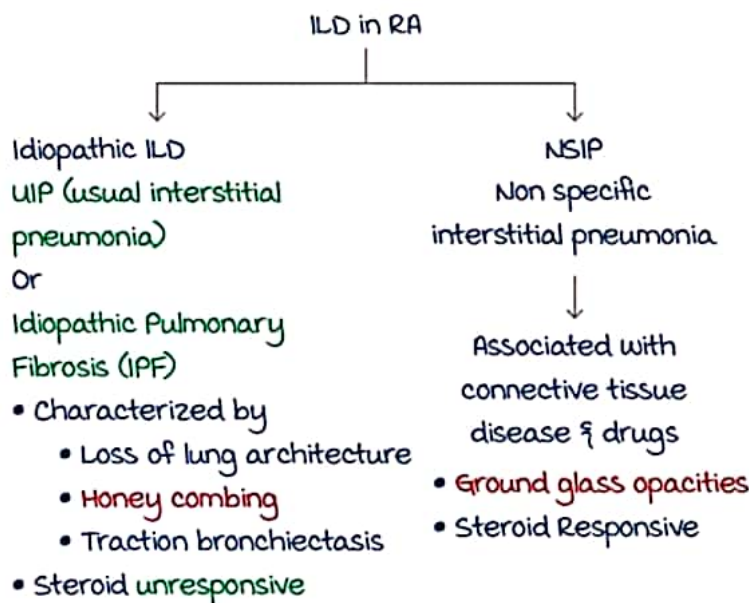


Pleural fluid pH < 7.2 – Suggestive of empyema

Interstitial lung disease in RA

00:42:35

- most dangerous complication in RA with respect to lung → Interstitial lung disease (ILD)



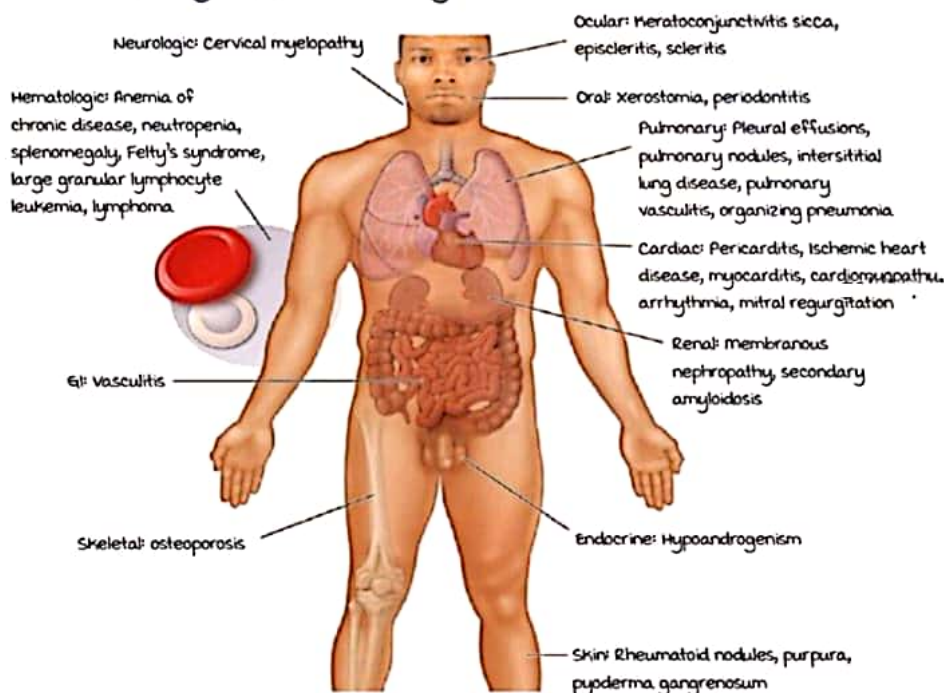
- UIP – universal interstitial pneumonia is the most common ILD in RA
- All the connective tissue disorders causes
↓
Lower lobe ILD's

Caplans syndrome

00:45:48

Nodules
+
Cavitation
+ Pneumoconiosis + RA } Caplans syndrome

- Indicates high disease activity

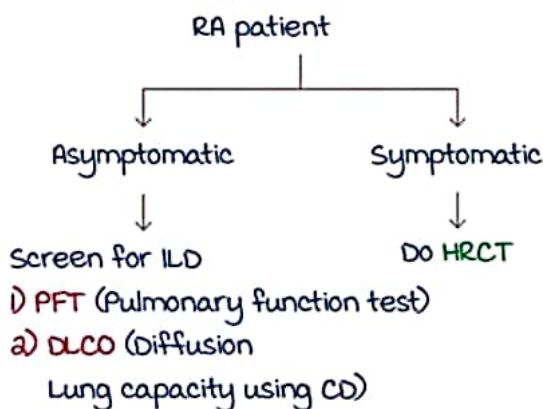


Active space

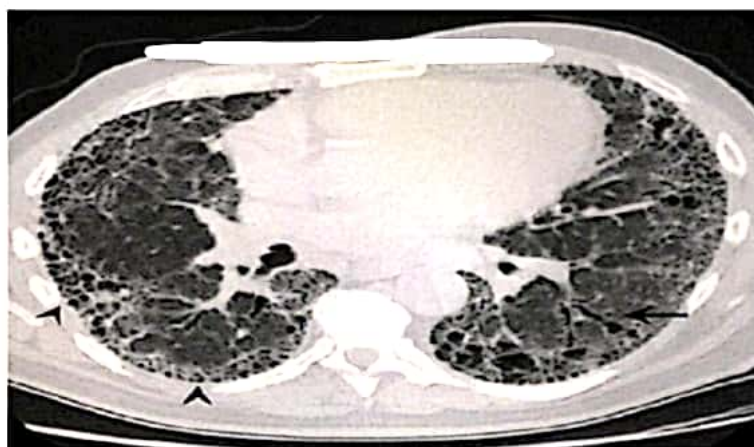
- ILD with decreased **DLCO** and $\frac{FEV_1}{FEC}$ Normal
- ILD can cause pulmonary Hypertension
- Two conditions that can produce nodules in the lung other than ILD } Wegener's silicosis

Symptoms in ILD:

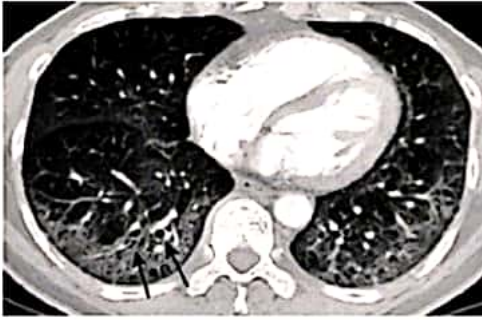
Dry cough
Exertional dyspnea



- Now, In Rheumatoid Arthritis → **UIP** (Universal Interstitial pneumonia)
- Response to treatment in ILD is **poor**



Bilateral, peripheral, and subpleural reticular infiltrates are evident. The presence of advanced fibrosis is indicated by honeycomb changes (arrowheads) and traction bronchiectasis (arrow).



- **NSIP** – Nonspecific interstitial pneumonia
↓
- Lung architecture is maintained
Ground glass opacities
- NSIP is seen in other connective tissue disorders

Rheumatoid vasculitis

00:50:29

- Long standing disease
- **RF Positivity**
- mononeuritis multiplex
- vasculitic ulcers
- Petechiae
- Purpura & gangrene
- Systemic features are uncommon
- RA patient came with Acute Abdominal pain

Proteinuria

Ascites

Here acute abdominal pain could be due to
Superior mesenteric Artery vasculitis



But there is no proteinuria

So, presence of proteinuria

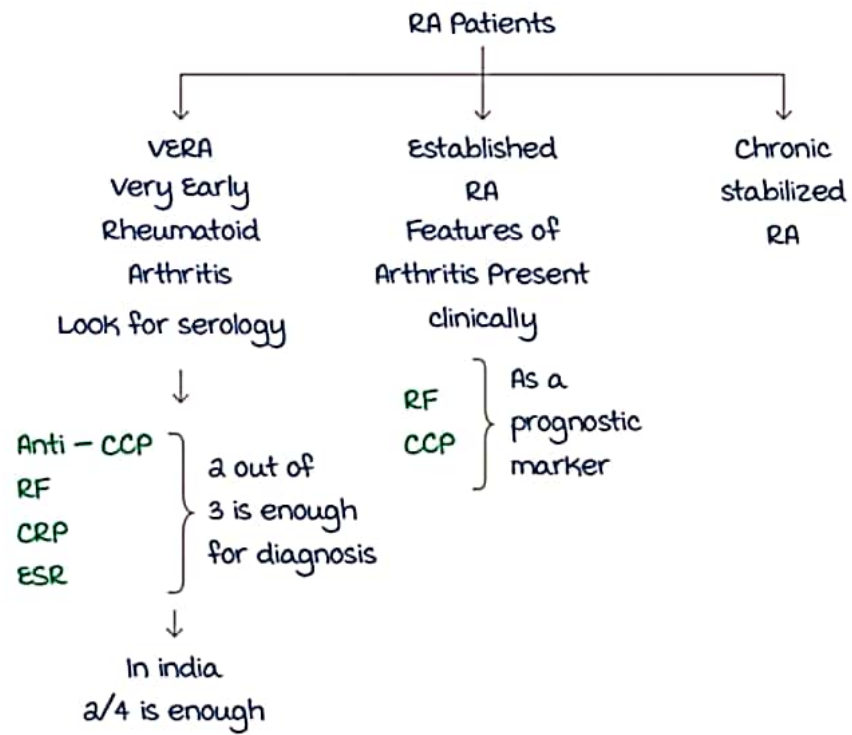


Indicates **2° Amyloidosis**

- Long standing disease
- It has a very bad prognosis
- methotrexate causes remission
- Cyclophosphamide in glomerular disease

RA – DIAGNOSIS AND MANAGEMENT

Criterion	Definition
1. Morning Stiffness	morning stiffness in and around the joints lasting at least 1 hr before maximal improvement
2. Arthritis of ≥ 3 Joint areas	At least 3 joint areas simultaneously having soft tissue swelling or fluid (not bony overgrowth alone) observed by physicians (the 14 possible joints areas are [right or left] PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)
3. Arthritis Of hand joints	At least 1 joint area swollen as above in wrist, MCP, or PIP joint
4. Symmetric Arthritis	Simultaneous involvement of same joint areas (as in criterion 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, observed by a physician
6. Serum Rheumatoid Factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive
7. Radiographic Changes	Changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)



Repeating RF & CCP → No value in follow up

Repeat CRP → For follow up



X-ray: Periarticular Osteopenias → Erosions



Management

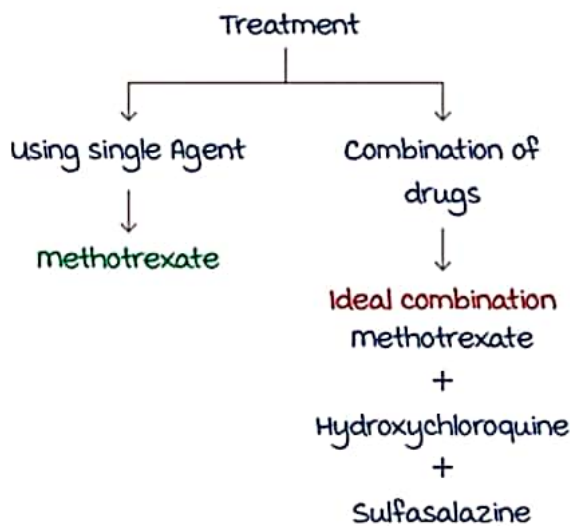
In VERA patient



DMARD's - Disease modifying Anti Rheumatoid Drugs

- Gold
 - D - Pencillamine
 - Azothioprine
 - Hydroxychloroquine
 - methotrexate
 - Sulfasalazine
 - Leflunomide
- } Not used now

DMARD of choice → methotrexate



- Leflunomide is a reserve drug
- Dose of methotrexate

↓
2.5 mg on Saturday & Sunday $\xrightarrow{\text{upto}}$ 25mg weekly dose

Remaining 5days → Folic Acid

methotrexate



- Dihydrofolate reductase inhibitor
- Dose dependent toxicity
 - ↳ Bone marrow Suppression
- mucositis - most common toxicity

Active space

Longterm methotrexate use → Dangerous complication
In Liver – **Hepatic cirrhosis**
In Lungs – **ILD** (Interstitial lung Disease)

2) **Hydroxychloroquine (HCQ)** – Dose of 200mg BD

- Causes **irreversible retinal Toxicity** in 1% of cases

3) **Sulfasalazine** – 2gm/day

4) **Leflunomide** –

- It is a Dihydro orotate dehydrogenase inhibitor
- Leflunomide also causes **hepatotoxicity**

So, in a VERA patient,

methotrexate 2.5mg on Saturday & Sunday

Or

methotrexate 2.5mg on Saturday & Sunday

+

Hydroxychloroquine 200mg BD

+

Sulfasalazine 2g/day

- **Disease activity** is followed up by → **CRP** (marker for follow up)

In case of **established RA** with clinical evidence of
Synovitis / Arthritis



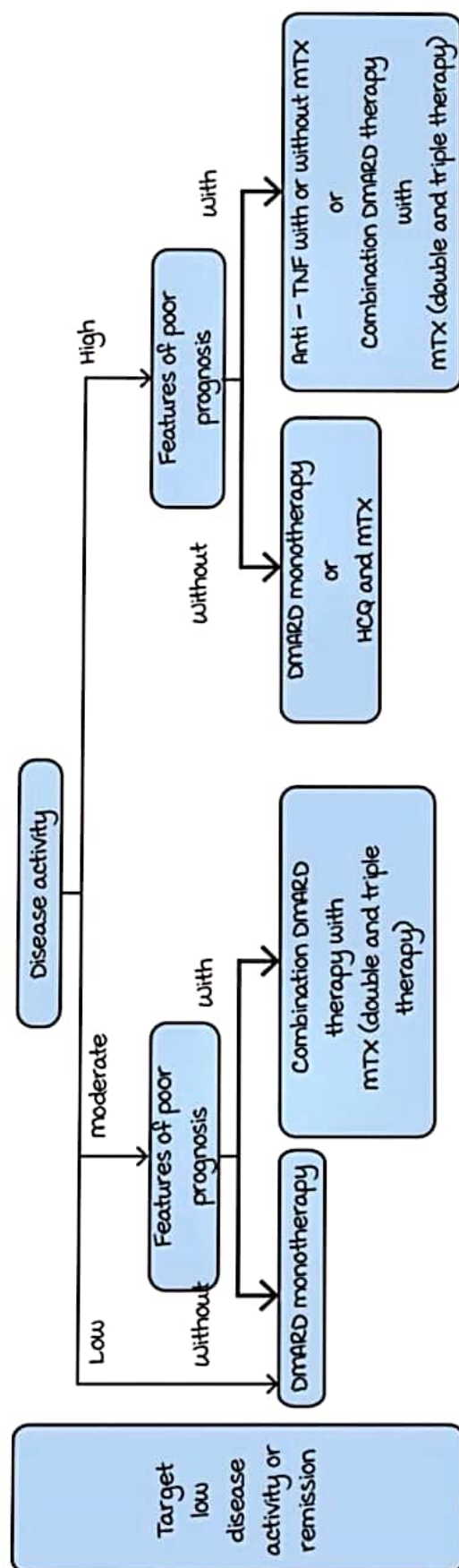
As DMARD's takes 6 – 8 weeks to achieve target
therapeutic level



Start **steroids**

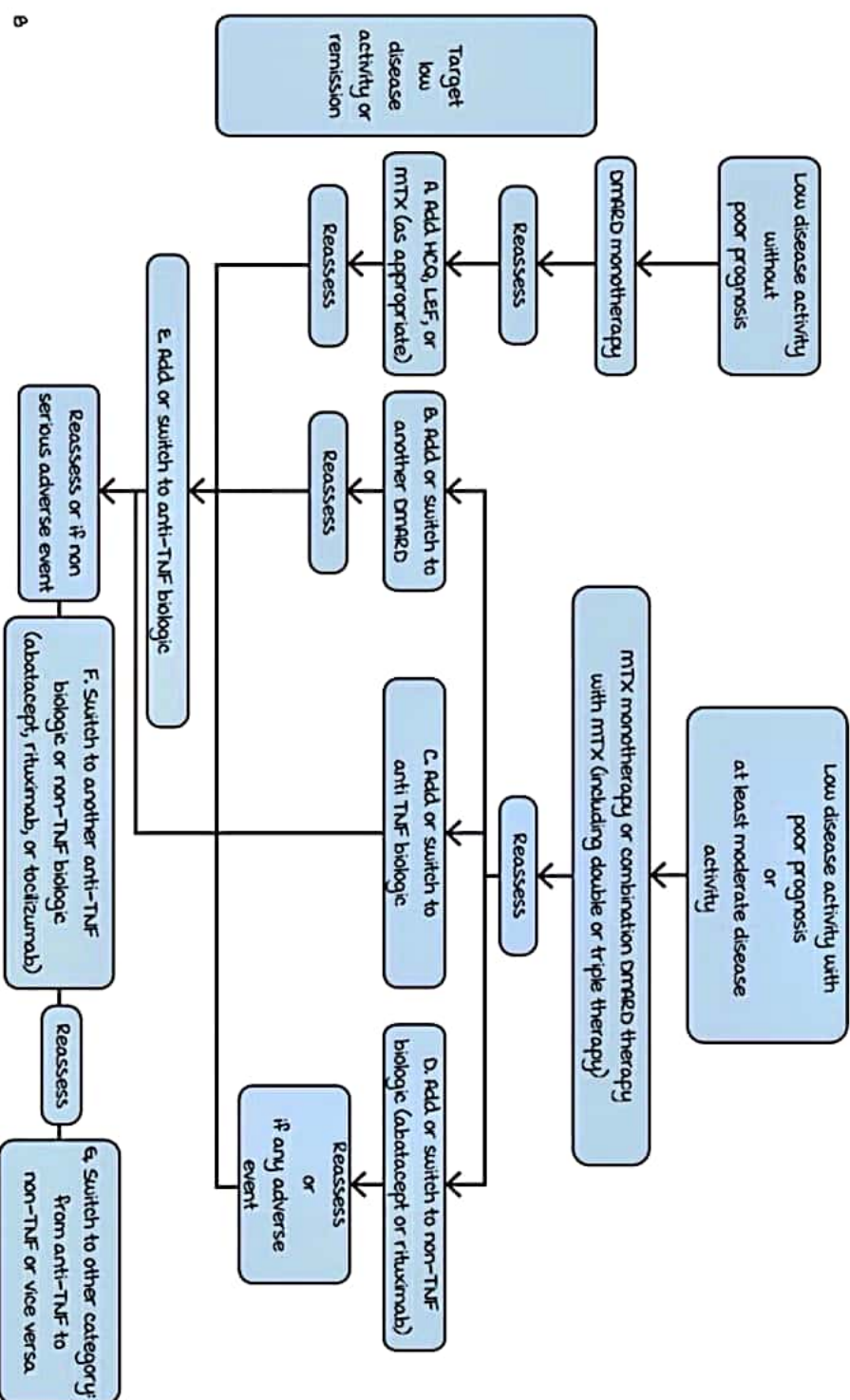


This is known as Bridge therapy



A

Active space



Early diagnosis & treatment

00:11:27

- Window of opportunity is 2yrs
↓
To be specific -3 month i.e, Pre-RA
- 1/3rd of undifferentiated arthritis → RA
- RF, CCP, CRP are used

IRA guidelines

00:12:41

- Never diagnose RA in the presence of monoarthritis
- Don't diagnose RA unless hands are involved
- If DIP joint is involved consider alternate diagnosis
- Lumbar spine is never involved
- RF (Rheumatoid Factor) never needs to be repeated
↓

Because it poorly correlates with Treatment

Biologics in RA

00:13:33

- Rheumatoid arthritis disease activity is high despite being on 2 or more DMARD's
- Biologics are used
- But Biologics have ↑ risk of infections
Contraindicated in pregnancy
(Hydroxychloroquine is the safest DMARD in Pregnancy)
- Biologics → Never use it alone
Always given along with DMARD's

1) Anti-TNF- α - Infliximab
 Etanercept
 Adalimumab
 Golimumab
 Certolizumab

- Anti -TNF α → risk of Drug induced SLE
 Hepatitis B flare
- Never start Anti -TNF - α with out ruling out latent TB

- Dose of infliximab - 3mg/kg I.V once every 2 weeks

2) Anti - CD20 - Rituximab

3) Anti - IL - 1 - Anakinra

4) Anti - IL - 6 - Tocilizumab

5) CTLA4 - IgG fusion molecule → Abatacept

CTLA4 - Cytotoxic T - cell Lymphocyte Associated Antigen - 4

6) JAK - 3 inhibitor - Tofacitinib

Table 1: DMARDs used for the treatment of rheumatoid arthritis					
Drug	Dosage	Serious Toxicities	Other common Side effects	Initial Evaluation	monitoring
Tocilizumab	4-8mg/kg IV monthly or 162mg SQ Every other week (<100kg weight). 162mg SQ every week (≥ 100kg weight)	Risk of Infection Infusion reaction LFT elevation dyslipidemia Cytopenias		PPD skin test	CBC and LFTs at regular intervals
Tofacitinib	5 mg orally BID	Risk of infection LFT elevation Dyslipidemia Neutropenia	upper respiratory tract infections Diarrhea Headache Nasopharyngitis	PPD skin test	CBC and LFTs and lipids at regular intervals
Abatacept	weight based <60kg: 500mg 60-100kg: 750mg >100kg: 1000mg IV dose at weeks 0, 2 and 4 And then every 4 weeks OR 125mg SQ weekly	↑ Risk bacterial, viral infections	Headache Nausea	PPD skin test	monitor for infusion reactions
Anakinra	100mg SQ daily	↑ Risk bacterial, viral infections Reactivation of latent TB Neutropenia	Injection site reaction Headache	PPD skin test CBC with differential	CBC every month for 3 months, then every 4 months for 1 year monitor for injection site reactions
Rituximab	100mg IV* 2, days 0 and 14 may repeat course Every 24 weeks or more Premedicate with methyl-prednisolone 100mg to decrease Infusion reaction	↑ Risk bacterial, viral infections infusion reaction Cytopenia Hepatitis B reactivation	Rash fever	CBC viral hepatitis panel	CBC at regular intervals

SPONDYLOARTHRITIDES

Seronegative spondyloarthropathy

- **Ankylosing spondylitis** or Bechterew's disease or Marie – Strumpell disease
- **Reactive arthritis** or Reiter's syndrome
- Psoriatic arthritis
- IBD or enteropathic arthritis
- Juvenile Idiopathic Arthritis (JIA)

Common binding features

00:02:06

- All of them are seen under 40 years (< 40 yrs)
- **Axial predominant** arthropathy
- **Rheumatoid factor RF** Negative
- HLA B27 – Positive
- males > Females
- most common extra articular manifestation → **Uveitis**
- Pathology: **Enthesitis**
Enthesis – site where ligament / ligament / tendon / joint capsule attaches to bone

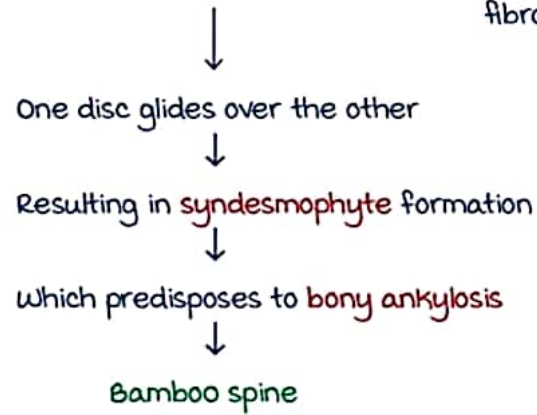
Ankylosing spondylitis

00:04:04

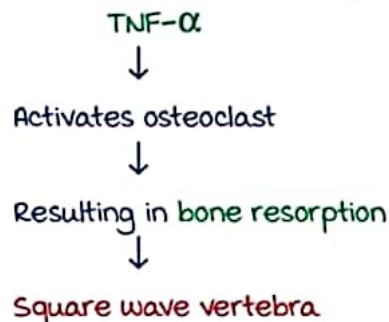
- male to female ratio is 3:1
- Generally diagnosed between 15–30 yrs
- **HLA B27** positive in 90–95% of adults
- **Axial inflammatory** arthropathy
- **Sacroiliitis** is the earliest manifestation with **enthesitis** (Achilles Tendinitis) with varying degree of peripheral joint involvement
+
Extra articular manifestations
- Key cytokine in ankylosing spondylitis is **TNF- α**

Active space

- Inflammatory granulation tissue (TNF- α) erodes the annulus fibrosus



- most common complication → spinal fracture



- Approach to the patient

Eg: 20 year old boy complains of back pain since 3 months

- mostly it is buttock pain

↓

Alternative buttock pain

- morning stiffness for > 30minutes
- Relieved with activity
- maximum pain in the early morning hours, disturbing sleep

And ESR } Elevated
CRP }

- Sacroiliitis is the earliest manifestation

↓

It can be asymmetrical

Table: Criteria for ankylosing spondylitis

Rome, 1961
Clinical Criteria
1. Low back pain and stiffness for more than 3 months, not relieved by 2. Pain and stiffness in thoracic region 3. Limited motion in lumbar spine 4. Limited chest expansion 5. History or evidence of iritis or its sequelae
Radiographic Criterion
6. Radiograph showing bilateral sacroiliac changes characteristic of ankylosing spondylitis (this excludes bilateral osteoarthritis of sacroiliac joints)
Define Ankylosing Spondylitis
Grade 3 or 4 bilateral sacroiliitis with at least one clinical criterion or At least four clinical criteria

ASAS classification criteria for axial SpA
(in patients with back pain ≥ 3 months and age at onset <45 years)

Sacroiliitis on imaging*
Plus
 ≥ 2 SpA features**

Or

HLA-B27
Plus
 ≥ 2 other SpA features**

**SpA features:

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease / ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

*Sacroiliitis on imaging:

- Active (Acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- Or
- Definite radiographic sacroiliitis according to mod. New York criteria

- To qualify as the criterion for inflammatory back pain of axial Spine the chronic (3 months) back pain should have four or more of these characteristic features
 - (1) Age of onset below 40 years
 - (2) Insidious onset
 - (3) Improvement with exercise
 - (4) No improvement with rest and
 - (5) Pain at night with improvement upon getting up



Earliest signs can be detected by 3-6 months after the onset

Sacroiliac Joints:

Early patches osteoporosis develop around the distal third of both the bones. Joint margins become illdefined and joint intervals become widened. Subchondral erosions starts and when there is multiple erosions, produces Rosary effect



Investigation of choice → MRI of spine

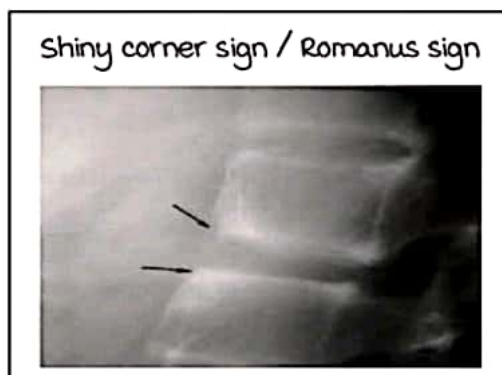
Bamboo spine



Radiology

00:13:13

- Earliest X-ray finding → Blurring of cortical margins of Subchondral Bone
- Sacroiliitis
- Bony erosions
- Bony ankylosis
- Calcification of Anterior interspinous ligament
↓
Dagger sign
- Calcification of Apophyseal joint capsule (pointed by black arrows in diagram)
↓
Trolley Track sign
- Shiny corner sign or Romanus sign

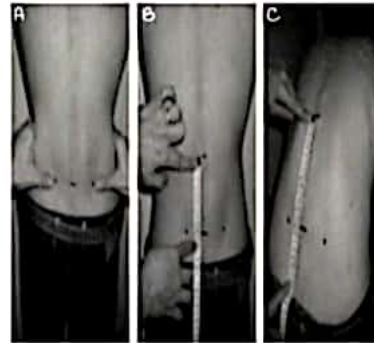


Active space

modified schober's Test:

- Palpate Posterior superior iliac spine (PSIS)
- Between the two PSIS → Sacral dimple

- In this test marks are made 5 cm below and 10 cm above the sacral dimples
- The distance between these marks should increase from 15 cm to at least 20 cm with lumbar flexion
- The distance less than 5 cm is abnormal



Extra articular features & peripheral joint involvement

00:16:55

involved are

Shoulder joint } Involvement predicts poor prognosis
hip joint }

Extra articular features

- most common - uveitis → acute anterior uveitis
- Cardiac manifestations → acute aortic regurgitation
Heart Blocks
- Lungs → Interstitial lung diseases (ILD)



Involves upper lobe

- Bronchiolitis obliterans
- most common ILD in ankylosis spondylitis → NSIP
(Non Specific Interstitial pneumonia)
- BOOP - Bronchiolitis Obliterans Organising Pneumonia



Pattern of ILD strongly associated with Ankylosing
spondylitis

- In axial skeleton involvement →
Cervical joints
 - Asymmetrical joint inflammation
 - **Syndesmophytes** → more marginal & delicate

- most characteristic
Or
diagnostic of
Psoriatic Arthropathy
↓
Ray pattern
- most often 2nd digit is involved



Ray pattern
PA Hand Note
the erosive
changes are
present at the
three joints of
the second
digit (arrows).
This pattern of
arthritis is
virtually
diagnostic of
psoriasis

Extra articular manifestations in psoriatic arthritis 00:47:02

- 1) most common – uveitis
↓
Bilateral chronic posterior uveitis
- 2) Lungs
 - upper lobe ILD → Nonspecific interstitial pneumonia
- 3) Kidney
 - a° IgA nephropathy
- 4) Heart
 - Aortic regurgitation
 - AV Blocks
- It is 100% clinical diagnosis

- Renal manifestations → 2° IgA nephropathy
- Skin manifestation → may have psoriatic lesions
- GIT → Inflammatory bowel disease like pathology

Management – AS

00:19:44

- mainstay of treatment → physiotherapy
- 1st line management → NSAID



Reverses the natural history of disease

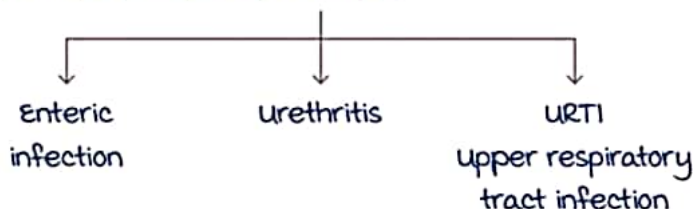
- Intra articular steroids for pain relief
- Sulfasalazine for peripheral arthritis
- Drug of choice → TNF- α Blockers

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Reactive arthritis / Reiter's syndrome

00:21:19

- Occurs after 1-4 weeks after infection



- most common cause in India *Shigella Dysenteriae*
- most common cause of urethritis worldwide



Chlamydia trachomatis

- Enteric infection caused by all the enteric Bacteria except *E.coli*
- Urethritis except *N. gonorrhoea* Can cause reactive arthritis
- URTI – upper Respiratory Tract Infection



β - hemolytic streptococci *Chlamydia pneumonia*



Can cause reactive arthritis

Table: microbial Infections Associated with Reactive Arthritis

Enteric Bacteria
Salmonella: various serovars
Shigella
S. flexneri
S. dysenteriae
S. sonnei
Yersinia
Y. enterocolitica (especially 0:3 and 0:9)
Y. pseudotuberculosis
Campylobacter
C. jejuni
C. coli
Clostridium difficile
Bacteria Causing Urethritis
Chlamydia trachomatis
mycoplasma genitalium [-]
ureaplasma urealyticum [-]
Bacteria Causing Upper Respiratory Infection
Beta-hemolytic streptococcus[-]
Chlamydia pneumonia

- Reactive arthritis following enteric infection



male to female ratio 1:1

- Reactive arthritis following urethritis

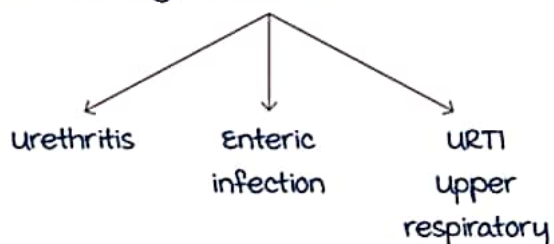


male to female ratio is 9:1

- Age of onset 15 - 30 yrs

male > female

- 1 - 4 week before, there is history of infection



- Presents with **mono or OligoArthritis**
 - Asymmetrical
 - Additive arthritis
 - Painful arthritis
- Starts predominantly in **lower limb** → knee
 - + ankle
 - + Subtalar
 - + metatarsophalangeal
- Risk for chronicity → **60%**

	Ankylosing Spondylitis	Reactive Arthritis
HLA B27	In 90% cases doesn't correlate with prognosis	In 70% cases Correlates with poor prognosis
Pain at Presentation	Doesn't correlate with bone fusion Pain is due to spasm Enthesitis (+++)	Doesn't correlate with chronicity Enthesitis (+)

Other features – reactive arthritis

00:27:40

- Inflammation of fingers & toes
 - ↓
 - Dactylitis**
 - ↓
 - Sausage digit**



Keratoderma blenorrhagica :



- Hyperkeratotic vesicles on the palms & soles which crusts
- Seen in 25% of patients
- most important differential diagnosis is pustular psoriasis



Keratoderma blenorrhagica

Circinate balanitis:



- Painless shallow erythematous ulcer on glans penis
- Seen in 25% of patients
- Rarely upper limb involvement in reactive arthritis
- Because in gonococcal arthritis → There is upper limb & lower limb involvement

Extraarticular features – Reactive arthritis

00:29:58

- 1) Acute Anterior uveitis
- 2) Cervicitis / Salpingitis/ urethritis
- 3) No risk of ILD
- 4) No axial Arthropathy
- 5) Cardiac → Aortic regurgitation due to aortic root dilatation
Heart blocks
- 6) 2° IgA nephropathy

- Reactive arthritis is completely clinical diagnosis
ESR } High
CRP }
- NSAIDs → Indomethacin - Drug of choice
- Reverses the disease course
- 60% of patients can go into chronicity
- HLA B27 → poor prognosis / chronicity
- If the disease goes into chronicity (Chronic reactive arthritis / Persistent Arthritis)



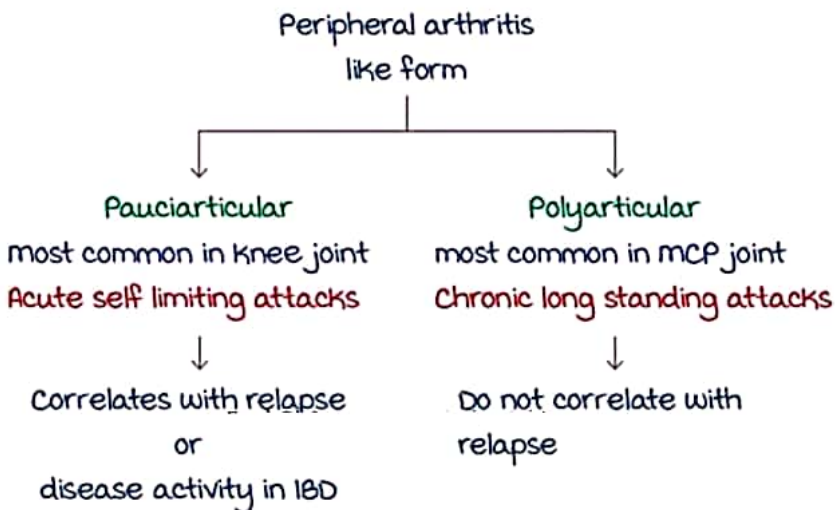
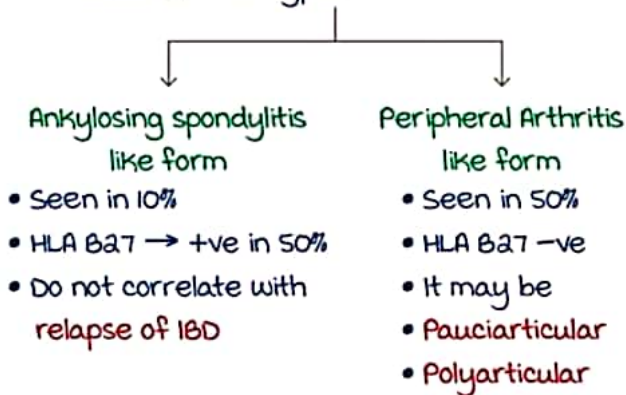
Drug of choice – Sulfasalazine

- Steroids are used only for intraarticular injection for pain relief
- No benefit of initiating Antibiotic therapy after development of arthritis

Enteropathic arthritis or IBD arthritis

00:33:25

- male to female ratio 1:1
- <30yr of Age
- most common in Crohn's disease > ulcerative colitis
- It can be of two types



- Enthesitis / dactylitis are very rare
- Poly articular arthritis is less common
- Infliximab is most effective

- 5-30% of patient with psoriasis develops arthritis

- Association

HLA Cw6 > HLA B27

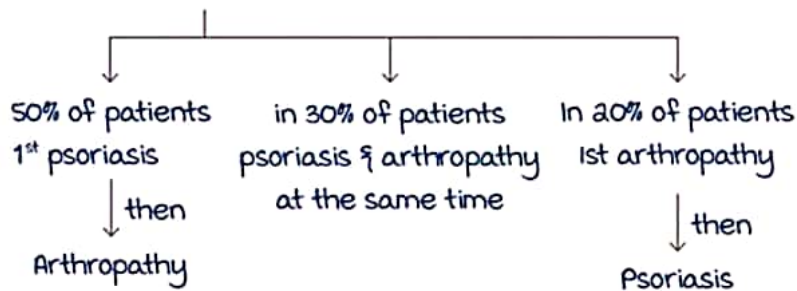
HLA B57

HLA DR7

HLA DQ-3

- Seen in 40-50 years males > Females

- 50/30/20 rule



- Dactylitis / enthesitis / nail changes are seen in every patients
- Nail changes are seen in 90%

A: Pitting of the fingernail. B: Onycholysis with an erythematous border



Nail changes

- 1) Nail pitting (most common)
- 2) Onycholysis
- 3) Horizontal ridging
- 4) Yellow nail changes
- 5) Dystrophic hyperkeratosis



Pattern of arthritis in psoriasis

- 1) Pure DIP joint arthritis
- 2) Symmetrical polyarthritis (2nd most common)
- 3) Asymmetrical mono & oligoarthritis (most common)
- 4) Axial arthropathy – **Cervical joints**

X-ray findings:

- Pencil in cup deformity
↓
Due to
Distal interphalangeal (DIP)
Joint involvement
Telescoping of digits



- marginal proliferative erosions
- Small-joint ankylosis
- Osteolysis of phalangeal and metacarpal bone, with telescoping of digits
- Periostitis and proliferative new bone at sites of enthesitis



- marginal erosions with adjacent bony proliferation (whiskering)

Arthritis mutilans



Severe joint destruction, especially at the metatarsophalangeal articulations, has resulted in fibular deviation and dorsal dislocation of the digits (Lanois' deformity). The presence of a pencil-in-cup deformity (arrow) at the interphalangeal joint of the big toe and osseous ankylosis of the first metatarsophalangeal and second and third proximal interphalangeal articulations (arrowheads) makes the diagnosis of psoriatic arthritis most likely

- In axial skeleton involvement →
Cervical joints
 - Asymmetrical joint inflammation
 - **Syndesmophytes** → more marginal & delicate

- most characteristic
Or
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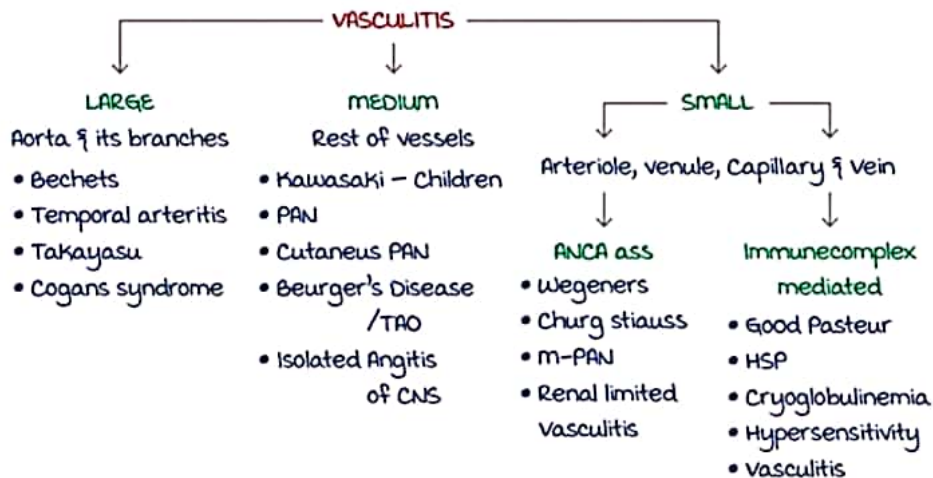
VASCULITIS : CLASSIFICATION & LARGE VESSEL

Introduction

00:00:49

Vasculitis: Inflammation within the vessel wall

- modified Chapel – Hill classification is used for vasculitis. It is based on the predominant size of the vessel involved.



Large vessel vasculitis

00:06:46

- It is a granulomatous inflammation within the vessel wall
- Predominantly CD₄ + T Helper cell mediated
 - i. Bechets
 - ii. Temporal arteritis(TA)
 - iii. Takayasu
 - iv. Cogans(triad) – Aortitis + Vestibulitis + Interstitial Keratitis

Temporal arteritis

00:08:00

- It is also called as Giant cell / Cranial / Granulomatous Arteritis
- Although giant cells are seen, it is not diagnostic of this condition
- Although called as cranial arteritis, extracranial vessels are also involved
- Along with this condition, Takayasu is also a granulomatous arteritis
- Full name: temporal arteritis polymyalgia rheumatica syndrome
- Seen only in > 50 years

- mean Age: 72 years
- F > m : 2 : 1
- $\frac{2}{3}$ rd of the patients are having associated polymyalgia Rheumatica (PMR)
- HLA DRB, O₄ - Important for TA & PMR
- MC vessel involved: superficial temporal artery
- 2nd mc : vertebral artery
- 3rd mc : ophthalmic artery
- 4th mc : posterior ciliary artery

Polymyalgia rheumatica (PMR): Pain & Stiffness especially in early in the morning in shoulder, neck & pelvic girdle

- ↑ in ESR >50mm/hr
- Excellent response to low dose steroids (10mg/day)

Clinical manifestations:

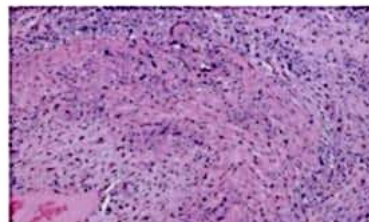
- 25% patients have non specific symptoms. They may present with
 - Pyrexia of unknown origin
 - Fatigue, weight loss
 - Jaw claudication - Specific
- 75% of patients present with head ache - mc
 - New onset headache in >50 years with ↑ in ESR (>100mm/hr)
 - 10% of patients are characterized by Tenderness of Temporal artery or ↓ pulsations
- It is associated with visual loss - unilateral or bilateral, temporary /Permanent- So, start the patient with steroids immediately after diagnosis of temporal Arteritis

American College of Rheumatology Classification Criteria for Giant Cell Arteritis

Criterion (*)	Definition
Age at disease onset ≥ 50 yr	Development of symptoms or findings beginning at age of 50 or older
New headache	New onset or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated erythrocyte sedimentation rate (ESR)	ESR ≥ 50 mm/hr by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

IOC: Temporal artery biopsy

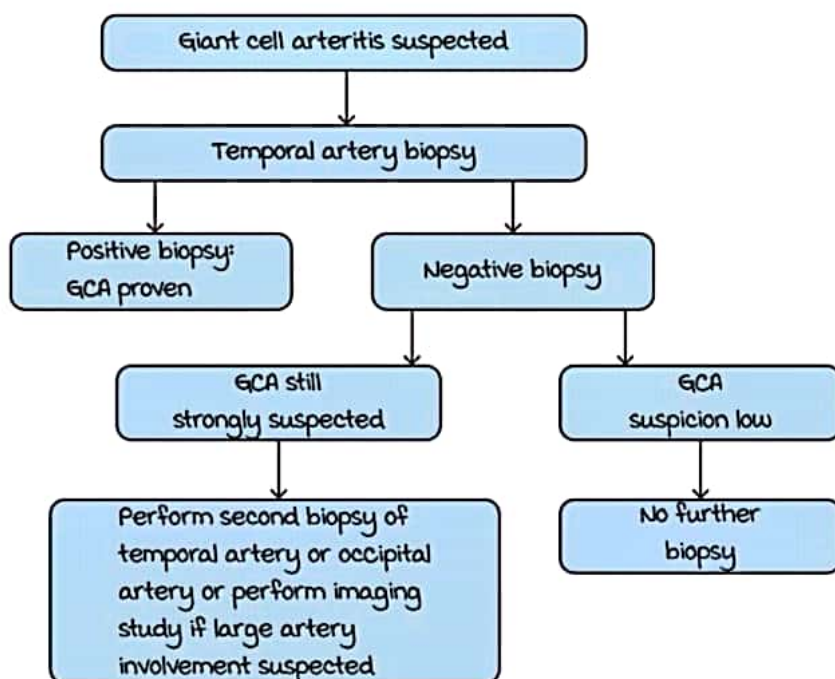
- Transmural Inflammation with mononuclear & giant cells



- Temporal arteritis is characterized by **skip lesions** So, if first biopsy is negative. It cannot eliminate TA completely
- Some patients may have visual field defects (VFD). When the posterior ciliary artery is involved, characteristic VFD is **Altitudinal hemianopia**. Very often associated with **Anterior Ischemic Optic Neuropathy (AION)** - characterized by the presence of pale swollen Optic Disc



management: 1mg/kg oral steroid + Low dose Aspirin
New drug: IL-6 Antagonist - tocilizumab



Takayasu arteritis

00:19:55

- Also k/a Pulseless Disease / non Specific aortoarteritis / Occlusive thromboaropathy
- mc vessel Involved: Subclavian Artery > Common carotid > Aorta > Renal > Superior mesenteric > Pulmonary > coronary
- Pulmonary & Renal are **never** Involved in Temporal arteritis, but they can be involved in takayasu
- Coronary - in 10% of cases
- Seen only in <50 years
- mean age: 24 years

- Young female with upper limb claudication → Check for pulse



Asymmetry in pulse



Check B.P (Asymmetry in B.P > 10 mmHg)



- Carotid / Subclavian / Aortic bruit
- IOC: CT Angiogram - shows occlusion / Stenosis / Aneurysm (rare)
- Associated aortic root dilation & aortic regurgitation may be seen
- As Renal artery is involved - Renovascular HTN is seen
- As Pulmonary artery is involved - Pulmonary artery HTN can be seen

Treatment:

- Steroids, Tocilizumab, Aspirin
- Poor prognosis as it is a progressive disease
- Renal involved - PTRR must be done (Percutaneous Transluminal Renal Angioplasty)

Comparison of Giant Cell Arteritis and Takayasu's Arteritis

Feature	Giant Cell	Takayasu's
Female-male ratio	2:1	8:1
Age range(yr)	50	<40
Average age of onset (yr)	72	25
Visual loss	10% - 30%	Rare
Involvement of aorta or its major branches	25%	100%
Pathology	Granulomatous arteritis	Granulomatous arteritis
Pulmonary artery involvement	No	Possible
Renal hypertension	Rare	Common
Claudication	Uncommon	Common
Ethnic groups with highest incidence	Scandinavians	Asians
Corticosteroid responsive	Yes	Yes
Bruits present	Minority	Majority
Surgical intervention needed	Rarely	Commonly

- It is called as **occulo oro genital Syndrome**
- most important manifestations: Oral cavity manifestations
+
2 out of 4
- 2 out of 4- Genital
Skin
Ocular
Pathergy test
- most often diagnosed by dermatologists as **80%** cases have skin manifestations
- Biopsy shows: **systemic perivascularitis with neutrophilic infiltration**
- m:F - 1:1 - but males have severe Disease
- HLA B5, B51
- Anti-saccharomyces cerevisiae antibodies (ASCA) - because of which bechets shows a lot of features similar to crohns with respect to bowel Involvement
- Anti selenium binding protein & Anti endothelium Ab (also seen in Kawasaki)

Oral cavity lesions:

- Characterised by recurrent Painful Aphthous ulcers with Shallow Necrotic base & can be seen anywhere In the Oral cavity & heals with out scarring
- Also known as **canker sores**



Genital ulcers:

- Not so recurrent
- more painful & heals with scarring
- Can be seen anywhere except Glans penis & urethra

Eye:

- Acute anterior / Posterior uveitis
- Retinitis

Pathergy test:

- Hypersensitivity to scratch / intra dermal saline

Systemic features:

- The most striking feature seen in Bechet's Diseases is thrombosis of venous > arterial



(Both superficial & Deep)

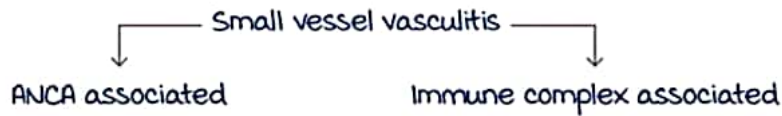
- It can involve CNS - K/a CNS bechets - characterized by venous strokes, brainstem arterial strokes
- Iliocolitis similar to crohns
- Small joint non erosive arthritis

Treatment:

- Mucocutaneous Disease - Topical steroids
- Arthritis - Hydroxychloroquine
- Severe mucocutaneous disease - Thalidomide / methotrexate
- Systemic Disease: Oral steroids + Azathioprine
- Bilateral panuveitis is very dangerous complication leading to blindness

VASCULITIS - MEDIUM & SMALL VESSEL

Small vessel vasculitis



ANCA associated vasculitis:

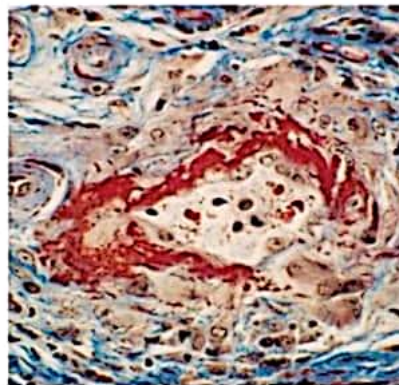
1. Wegener's: Granulomatosis with polyangitis (GPA)

- Necrotising vasculitis with Fibrinoid Necrosis (NVFN) + Granuloma + C-ANCA (70%) + P-ANCA (25%)

2. Churg - Strauss: Allergic/ Eosinophilic GPA (AGPA/EGPA)

- NVFN + Eosinophils + Tissue eosinophilic infiltrate + extra vascular granuloma + C - ANCA (5%) + P - ANCA (40%)

NVFN



3. m - PAN (microscopic PAN): NVFN without Granuloma

- P - ANCA (50%) + C - ANCA (40%)

4. Renal Limited Vasculitis

- Masson's trichrome stain is used in the image above to stain NVFN

- Red colour - Fibrinoid necrosis

Differentiating small vessel vasculitis based on anca studies 00:03:40

- ANCA - Anti Neutrophil Cytoplasmic Ab
- Screening ANCA is by Immunofluorescence
 - i. Cytoplasmic pattern (C - ANCA)
 - ii. Nuclear pattern or perinuclear pattern (P - ANCA)

- Confirmation is by ELISA
 - For cytoplasmic pattern - Proteinase 3 Ag is checked. It is seen in Granules of Neutrophils
 - For perinuclear pattern - MPO is checked. It is seen in the lysosomes of monocytes

Conditions with predominant C-ANCA positive

00:05:33

ANCA in Small - vessel vasculitis			
Disorder	Proteinase 3 (PR3, usually c-ANCA)	Frequency (%) myeloperoxidase (MPO, usually p-ANCA)	Negative
Granulomatosis with polyangiitis (Wegener)	70	25	5
microscopic polyangiitis	40	50	10
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	5	40	55
Renal - limited Pauci-immune Crescentic GN	20	70	10

1. Wegeners - 70% +ve
 2. m-PAN - 40% +ve
 3. Renal limited vasculitis - 20% +ve
 4. Churg - Strauss - 5% cases +ve
- ANCA titers do not correlate with relapse

Conditions with predominant P-ANCA positive

00:06:49

1. m-PAN - 50%
 2. Renal limited vasculitis - 70% P-ANCA +ve
 3. Churg Strauss - 40%
 4. Wegeners - 25%
- Drugs induced P-ANCA +ve - Hydralazine, Propylthiouracil

False +ve P-ANCA:

- Target antigen is not MPO
- Seen in
 - a. Rheumatoid Arthritis
 - b. IBD
 - c. Infective Endocarditis

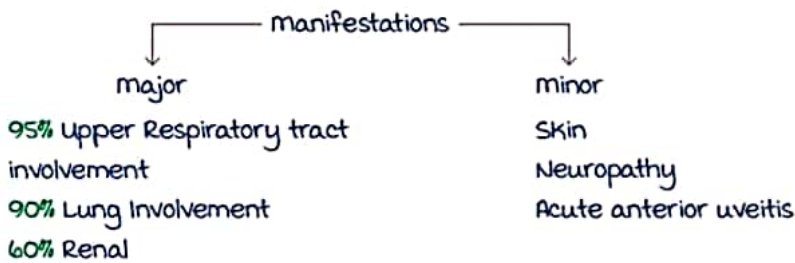
- d. Autoimmune Hepatitis
- e. Goodpasture Syndrome
- f. Primary Sclerosing cholangitis

- Goodpasture may produce ANCA even due to P-ANCA

Wegener's GPA

00:10:55

- NVFN + Granuloma + C > P-ANCA
- HLA DP B 104
- > 40years, m : F = 1 : 1



Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

i. 95% upper respiratory tract involvement:

- Can be seen in 4 forms
 - a. B/L serous otitis media with deafness
 - b. midline nasal deformity
 - c. Recurrent sinusitis due to staph aureus
 - d. Subglottic stenosis

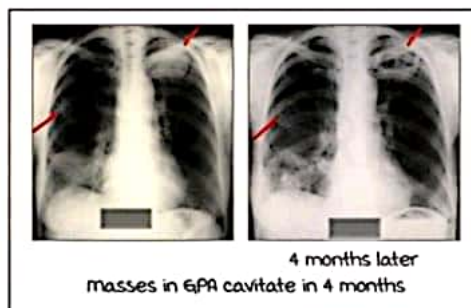
ii. 90% Lung Involvement

- Can be seen in 2 forms

Diffuse Alveolar Hemorrhage (DAH)



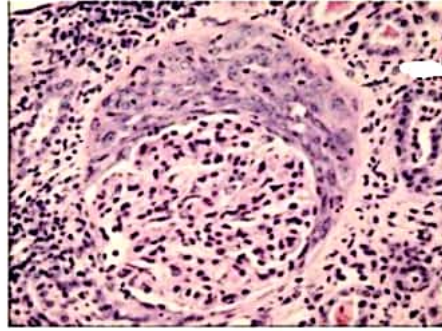
Cavitating Nodules with Thick walls



Active space

iii. Renal Involvement

DPGN + crescents → RPGN



minor manifestations:

1. Small fiber Neuropathy – Similar to D.M
2. Acute anterior uveitis
3. Skin lesions – Petechiae or purpura/ Vesicae or bullae

Pathological features of Wegeners:

- Geographical necrosis
- Palisading histiocytes

M – PAN

00:15:40

- > 40 years
- m > F
- No granuloma is seen
- P – ANCA – 50% , C – ANCA – 40%

major manifestations:

i. Kidney: Gets involved in 100% of patients – Type III RPGN



On Biopsy: DPGN + crescents

- ii. Lung: 50% of patients – Only DASH, no nodules
- iii. URT: 30% – Sinusitis due to Staph aureus
- iv. Fever & Constitutional symptoms are more common

minor manifestations:

1. Cutaneous manifestations are more common when compared with Wegeners
2. Neuropathy is less severe
3. Uveitis – not seen
4. mesenteric artery involvement- may be seen leading to bowel ischemia

Churg – Strauss syndrome

00:18:41

- EGPA or AGPA
- NVFN with Extravascular Granuloma
- It has 3 phases

i. Allergic/Asthmatic phase/Prodromic phase:

- Behaves just like Bronchial asthma with allergic rhinitis.

ii. Eosinophilic Phase:

- Repeated episodes of bronchial asthma
- B/L fleeting lung infiltrates
- Disproportionate Eosinophilia

iii. Vasculitis phase:

- Skin lesions suggestive of vasculitis.
- Cardiac Involvement – MCC of Death
- Severe neuropathy
- Renal: RPGN type III but very mild

Differential diagnostic features of the antineutrophil cytoplasmic antibody – associated vasculitis

Feature	Wegener's Granulomatosis	microscopic Polyangiitis	Polyarteritis Nodosa	Churg-Strauss Syndrome	Comments
Pulmonary Infiltrates Or nodules	+++	++	-	+++	Asthma and eosinophilia in CSS
Alveolar hemorrhage	++	++	-	+	
Glomerulonephritis	+++	+++	-	++	Progressive renal failure uncommon in CSS
upper airway disease	+++	+	+	++	ENT disease usually favours
Skin, Purpura	+	+++	-	++	
Peripheral nervous system involvement	++	+	++	+++	Often a prominent feature of CSS
central nervous system involvement	+	+	+	++	

Treatment of anca associated vasculitis:

- i. High dose I.V steroids for 3 days + Oral steroids tapered over 4-6 wks
+
Oral cyclophosphamide - 6 months

Relapse: rituximab

Maintenance: Low dose steroids + Azathioprine or MMF

- ii. For mild disease: methotrexate may be used
- iii. For severe lung hemorrhage or CNS vasculitis - plasma exchange

Poly Arteritis Nodosa (PAN)

00:25:10

- Involves only medium sized vessels
- Seen in 5th - 6th Decade
- m > f
- BAD prognosis
- Commonly associated with Hep B & Hairy cell leukemia
30/1 rule: 30% of patients with PAN are HBsAg positive but 1% of patients with HBsAg are having PAN
- It produces micro aneurysms than occlusion of medium sized vessels
- Glomerular/pulmonary capillaries are not involved - So, DAP / Glomerular nephritis is Not seen in PAN
- Classically it causes Renal Artery microaneurysms So, it produces typical features of Renovascular HTN
- It can produce mesenteric & testicular artery occlusion - testicular pain
- Patients presents with HTN with disproportionate target organ damage because of renovascular HTN
- Skin lesions: Nodules, ulcers, Gangrenous, mononeuritis multiplex
- MR/CT Angiogram: microaneurysms are seen
- Constitutional symptoms: +++ with fever & weight loss

ACR criteria for PAN: (ACR)

1. Weight loss > 4kg
2. Livido reticularis
3. Testicular pain
4. mononeuropathy

5. Systemic HTN
6. HBsAg
7. Aneurysm on arteriogram
8. Biopsy: necrotising vasculitis with granulocyte & monocytes in arterial wall
 - It is steroid refractory

Other medium vessel vasculitis:

- Kawasaki
- Thromboangitis obliterans/Buerger's disease.

Immune complex mediated small vessel vasculitis

00:32:17

1. Goodpasture syndrome
2. HSP
3. Cryoglobulinemia
4. Hypersensitivity vasculitis / Cutaneous leukocytoclastic angiitis

Henoch Schonlein Purpura (HSP)

00:33:14

- It is now called as Henoch - Schonlein vasculitis / IgA vasculitis
- mc vasculitis in children
- Seen in < 20yrs, m > F
- Peakage: 4 - 7 years

4 Systems Involved:

1. Skin - 100% involved
2. Joints - 50%
3. G.I.T - 70%
4. Kidney - < 10% of patients



- i. Skin : Non - thrombocytopenic palpable purpura, predominantly in lower limb extensor aspect
- ii. Joint : LMN Arthritis (large joint migratory Non deforming)
- iii. GIT: Acute Abdominal pain (Abd. angina) - Blood in stool, vomiting, Intussusception (rare), Erosive Hemorrhagic Duodenitis
- iv. Kidney : IgA nephropathy, Seen in adult HSP Glomerulonephritis

Biopsy from skin lesions: Only for Arthralgia & Abdominal

Pain – Steroids are used

→ vessel wall Granulocytes & IgA predominant on IF

Essential mixed cryoglobulinemia

00:36:42

- Cryoglobulins are cold precipitated immunoglobulin. It is classified as Type 1, 2 & 3
- 70% of patients are having **Hepatitis C**. It is closely associated with Hep C
- It is immune complex mediated small vessel vasculitis
- 40 – 60y, m > F

Type 1: Purely monoclonal, It is plasma cell disorder, – monoclonal IgM/IgG

Type 2: Combined polyclonal IgG & monoclonal IgM } Seen in

Type 3: Purely Polyclonal

- Hep C
- Sjogren
- SLE

Types of cryoglobulins

cryoglobulin	Rf positivity	monoclonality	associated disease
Type I	NO	Yes (IgG or IgM)	Hematopoietic malignancy (multiple myeloma, waldenstrom's)
Type II	Yes	Yes (polyclonal IgG, monoglona IgM)	Hepatitis C Other infection Sjogren's syndrome SLE
Type III	Yes	No (polyglonal IgG and IgM)	Hepatitis C Other infection Sjogren's syndrome SLE

Clinical manifestations:

Skin : Non – Thrombocytopenic

Palpable Purpura

Confluent purpura

Extremity ulcers

Joint: small joint, upper limb - non erosive arthritis

Kidney: MPGN

GIT : Hep-C & peripheral neuropathy

Treatment: treat hepatitis -C

Secondary vasculitis

00:42:27

1. Drugs : ANCA +ve : Hydralazine, PTU

2. Rheumatological: SLE, RA, Sarcoid

3. Infectious : Histoplasmosis, Rickettsiae,
HepB - PAN
HepC - Cryoglobulinemia

MINERAL DEFICIENCIES

Copper deficiency :

- microcytic hypochromic anemia
- Hair defects - Defective Keratinisation and pigmentation
- Growth retardation
- Defective elastin
- Mental retardation
- Osteoporosis

Copper toxicity : Hepatotoxicity
Hemolytic anemia

Chromium deficiency : Impaired glucose tolerance.

Phosphorus deficiency :

- Rhabdomyolysis
- Hemolysis
- Ataxia
- Seizure

Zinc deficiency :

- Growth retardation
- Alopecia
- Ageusia
- Anosmia
- Gonadal dysfunction
- Dermatitis
- Immune dysfunction

Zinc toxicity : Pulmonary fibrosis

manganese deficiency :

- Lipid + Carbohydrate metabolism - altered
- Growth and skeletal developmental retardation
- Upper body rash

Iron deficiency :

- Impaired cognition
- Poor work performance
- Premature labor
- Increased perinatal deaths

Deficiency

Selenium deficiency :

Seen in Keshan disease

Causes Hypothyroidism in Sub himalayan zone

molybdenum deficiency :

Neurological Symptoms + oesophageal cancer

Toxicity / overdose

00:04:00

- **manganese overdose** : Parkinsonism like features.
- **Boron overdose** : Developmental defects
 - male sterility
 - Testicular atrophy
- Iron toxicity : **Increased susceptibility to malaria**
- Lead toxicity : Gout , tubulointerstitial disease
 - Saturnine gout** / Lead nephropaty - **hyperuricemia**
- Cadmium toxicity : Nephrotoxicity with severe bone pain
 - (**Ouch Ouch nephropathy**)
- **Chromium toxicity** : Renal failure + lung cancer
- **Arsenic toxicity** : Peripheral neuropathy
 - Garlic like odour
 - Lung and nasal cancers
- **Fluorine toxicity** : Calcification of tendon / ligament
 - Exostoses

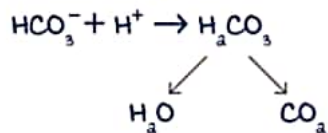
ACID BASE REGULATION - 1

Chemical buffer system

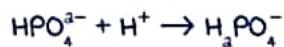
00:03:33

- Bicarbonate buffer system ← **most efficient**
 - Phosphate buffer system
- } Extracellular buffers

- pK_a of $HCO_3^- = 6.1$ (weak acid)



- pK_a of $HPO_4^{2-} = 6.8$ (weak acid)

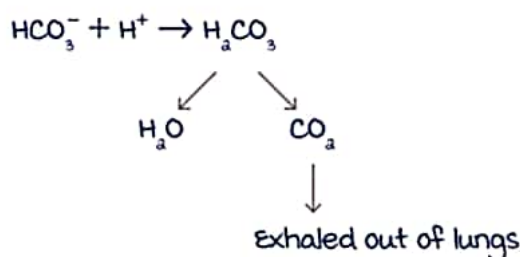


- When a molecule has got a pK_a which is close to the physiological pH it will be an effective buffer
- Intracellular buffer
 - Proteins $\rightarrow$ Hb
 - Phosphate

Respiratory buffer system

00:11:52

- Exhaling or retaining of CO_a in response to extracellular pH



Renal buffer system

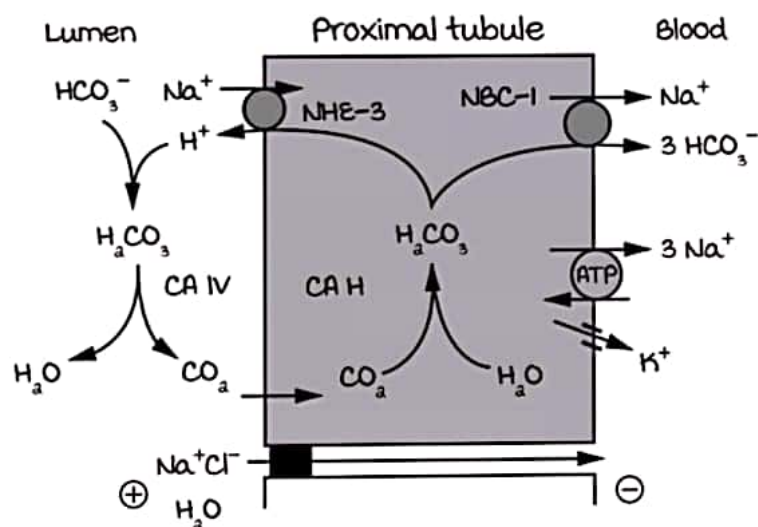
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- 80 meq of non volatile acids are produced per day, excreted by kidney
- 4320 meq of HCO_3^- filtered / day at glomerulus
- For every molecule of HCO_3^- reabsorbed, **one H^+ is excreted**
- Total H^+ excreted / day $\rightarrow 4320 + 80 = 4400$ meq

- For excretion of 4400 meq H^+ $\rightarrow$ >2500 lts of urine /day
- $\therefore$ The management of H^+ excretion done by urinary buffers
- Ammonia buffer (NH_4^+)
- Phosphate buffer
- $pK_a = pH$ at which associated form = dissociated form
 $HA = A$
- Henderson equation:
$$pH = pK_a + \log \frac{A}{HA}$$
- Bicarbonate generation = net acid excretion in urine = 70-80 meq / day
- Acid is getting excreted in the form of:
 - Ammonium (NH_4^+)
 - Titratable acid (phosphate / creatinine / butyrate)
- $\therefore NAE = NH_4^+ + \text{Titrateable acid} = 70-80 \text{ meq / day}$

Bicarbonate at the proximal tubule

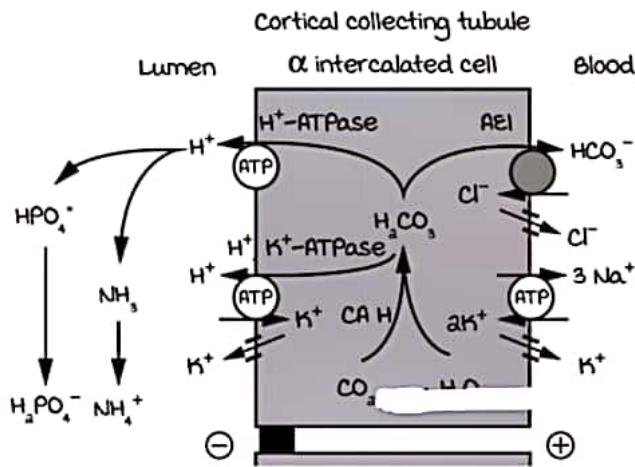
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Acidification of urine

00:29:50

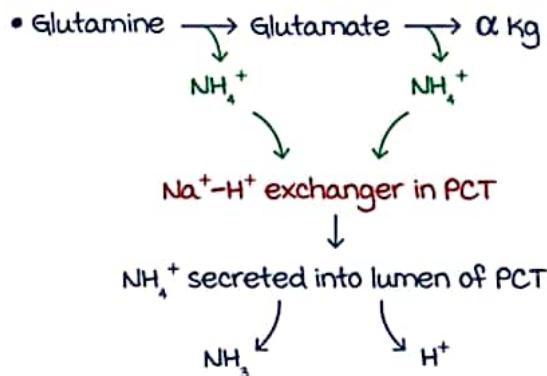
- Acidifying machinery → Cortical collecting tubule
↳ α intercalated cells



Ammonia recycling

00:33:21

- Ammonium synthesis & excretion is the most important way kidneys eliminate non volatile acid
- Formation of ammonia:



- In response to $\uparrow$ acid load kidney compensates by $\downarrow$ $\uparrow$ Ammonia excretion
- Stimuli of ammonia production $\rightarrow$
 - metabolic acidosis
 - Hypokalemia

- NH_3^+ at thick ascending limb $\rightarrow \text{Na}^+\text{K}^+\text{ATPase} \rightarrow$ reach the interstitium
 $\downarrow$
 $\text{NH}_4^+ \leftarrow \text{urine} \leftarrow \text{Collecting duct}$

- pKa of ammonia $\rightarrow 9.2$. $\therefore$ at physiological pH 98% is NH_4^+
- Ammonia generated in the kidney $\rightarrow \text{NH}_4^+$

Acids in the body

00:42:49

- 2 types
- Volatile acids
 - Formed by metabolism of
 - carbohydrates
 - Fat
 - Proteins
 - Excreted as CO_2 from lungs
- Non volatile acids: (fixed acids)
 - Formed by metabolism of
 - Phospholipid
 - Nucleic acids
 - Ex: Sulphuric acid, phosphoric acid, organic acids
 - Excreted by kidneys
- According to Henderson Hasselbach's equation, important determinants of H^+ $\rightarrow$ Bicarbonate (22.26 meq/L)
 - PCO_2 (40 mmHg)
- 1st defence $\rightarrow$ Chemical buffer
- 2nd defence $\rightarrow$ Respiratory buffer
- 3rd defence $\rightarrow$ Renal buffer

Metabolic acidosis

00:49:07

- Heart:
 - $\downarrow$ myocardial contractility
 - Sympathetic overactivity
- CNS
 - Lethargy, disorientation, stupor, coma

- Hyperventilation
- Hyperkalemia
- $\text{measured cations} + \text{unmeasured cations} = \text{measured anions} + \text{unmeasured anions}$

$$MC + UC = MA + UA$$

$$MC - MA = UA - UC$$

$$Na^+ - (Cl^- + HCO_3^-) = UA - UC$$

$$\begin{aligned} \text{Anion gap} &= UA - UC \\ &= 8-12 \text{ meq / L} \end{aligned}$$

- $\text{Corrected anion gap} = \text{Anion gap} + 2.5 (4.5 - S. \text{Albumin})$
- Classification of metabolic acidosis:
- High anion gap MA:
 - Ketoacidosis → • DM
 - Alcohol
 - Starvation
 - Lactic acidosis
 - Uremic acidosis
 - methanol / ethylene glycol
 - Salicylate / paraldehyde
- Normal anion gap MA:
 - Renal acidification defect → RTA
 - GI loss of HCO_3^- → • Diarrhoea
 - Small bowel tumor
 - ureterosigmoidostomy
 - Anion exchange resins
- **Hyperchloremic metabolic acidosis**

Metabolic alkalosis

01:03:13

- Heart:
 - Cardiac arrhythmias
- Brain
 - Cerebral insufficiency

- Hypocalcemia
- Hypokalemia
- Hypomagnesemia
- Classification of m. alkalosis:
- Chloride or Saline sensitive/ responsive :
 - urinary $\text{Cl}^- < 15 \text{ meq /L}$
 - Vomiting
 - Nasogastric suctioning
 - Long term diuretic use
 - Cystic fibrosis
 - Post hypercapnia
 - pyloric stenosis
- Chloride unresponsive: saline resistant
 - urinary $\text{Cl}^- > 15 \text{ meq /L}$
 - With HTN → RAS activation
 - ↳ Aldosterone tumors
 - Liddle syndrome
- Without HTN →
 - Recent diuretic use
 - Bartter syndrome
 - Gitelman syndrome

ACID BASE REGULATION - 2

ABG - Arterial blood gas precautions

00:00:36

- Abnormal modified Allen test
- Local infection / distorted anatomy at the puncture site
- Severe peripheral vascular disease of the artery
- Active Raynaud's syndrome

ABG - Procedure and precautions

00:01:10

- Preferred artery →
 - Radial A
 - Femoral A
- 21 gauge needle
- Flush the syringe with 0.5 ml of 1 : 1000 heparin
- Don't leave excess heparin in the syringe → ↓ HCO_3^- , ↓ PCO_2
- Ensure no air bubbles
- Early analysis & transported via cold chain

Estimation of H^+ from pH

00:04:47

- As the pH ↑ → H^+ ↓
- pH 7.4 → H^+ → 40
- 7.3 → 50
- 7.5 → 32

Normal values of ABG

00:06:32

- pH → 7.36 - 7.44 (7.40)
- HCO_3^- → 24-26 mEq/L (24)
- PCO_2 → 35-45 (40)
- H^+ → 36-44 meq/L (40 nEq/L)
- pH < 7.2 → Severe acidosis
- pH > 7.6 → Severe alkalosis

- Obtain ABG & serum electrolytes simultaneously
- $\text{HCO}_3^- = 24 \times \frac{\text{PCO}_a}{\text{H}^+}$
- measured HCO_3^- is compared with HCO_3^- of venous blood
- For ABG to be compatible
The measured HCO_3^- should be within ± 2 values compared to HCO_3^- of venous blood

Interpretation of ABG

00:13:00

- pH $\rightarrow > 7.40 \rightarrow$ Alkalosis
 $< 7.40 \rightarrow$ Acidosis
 $7.40 \rightarrow$ Normal / mixed ABG
- Respiratory or metabolic component has changed in the direction of pH
 - Ex: pH - 7.32 $\downarrow$ (7.40) Acidosis
 HCO_3^- - 16 $\downarrow$ (24) Acidosis
 PCO_a - 35 $\downarrow$ (40) Alkalosis
 - metabolic acidosis
pH - 7.46 $\uparrow$ (7.40) Alkalosis
 PCO_a - 25 $\downarrow$ (40) Alkalosis
 HCO_3^- - 20 $\downarrow$ (24) Acidosis
 - Respiratory alkalosis
- Compensation for metabolic acidosis
 - By respiratory alkalosis
 - $\text{HCO}_3^- \downarrow$ by 1 meq/L = $\text{PCO}_a \downarrow$ by 1.2 mmHg
 - Ex: pH - 7.10
 PCO_a - 32
 HCO_3^- - 10
metabolic acidosis

HCO_3^- - fall from 24 $\rightarrow$ 10 = 14 meq/L fall

$$\therefore \text{compensation} = 14 \times 1.2$$

$$= 17$$

$$\therefore \text{The expected } \text{PCO}_2 = 40 - 17 \\ = 23$$

- $\therefore$ It is uncompensated or partially compensated metabolic acidosis
- $\therefore$ in the given problem PCO_2 is 32 & the expected PCO_2 is 23 & hence there is uncompensation

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

ACID BASE REGULATION - 3

Compensation

00:06:20

- metabolic acidosis:
 - $\text{HCO}_3^- \downarrow$ by 1 meq /L = $\text{PCO}_a \downarrow$ by 1.2 mmHg
- metabolic alkalosis:
 - $\text{HCO}_3^- \uparrow$ by 1 meq /L = $\text{PCO}_a \uparrow$ by 0.7 mmHg
 - Ex:

$$\text{pH} = 7.43 - \text{Alkalosis}$$

$$\text{HCO}_3^- = 32 - \text{Alkalosis}$$

$$\text{PCO}_a = 40 - \textcircled{\text{N}}$$

= metabolic alkalosis

- Increase in $\text{HCO}_3^- = 32 - 24 = 8$
- Expected $\uparrow$ in $\text{PCO}_a = 8 \times 0.7$
= 5.6

$$\therefore \text{Expected } \text{PCO}_a = 40 + 5.6 = 45.6 \text{ mmHg}$$

$\therefore$ it is uncompensated metabolic alkalosis

- pH = 7.30

$$\text{HCO}_3^- = 14$$

$$\text{PCO}_a = 20$$



met. Acidosis
+
Resp. Alkalosis

$$\text{PCO}_a = 28$$



met. Acidosis
fully compensated
or
Simple metabolic
acidosis

$$\text{PCO}_a = 35$$



met. Acidosis
partially
compensated

$$\text{PCO}_a = 42$$



met + Resp
acidosis

- Winters formula for metabolic acidosis:

$$\text{PCO}_a = 1.5 \times \text{HCO}_3^- + 8 \pm 2$$

Active space

• Respiratory

1 4 → Resp. Acidosis

2 4 → Resp. Alkalosis

• Respiratory acidosis:

• Acute resp. Acidosis → $PCO_2 \uparrow$ = $HCO_3^- \uparrow$
10 mmHg 1 meq/L

• Chronic resp. Acidosis → $PCO_2 \uparrow$ = $HCO_3^- \uparrow$
10 mmHg 4 meq/L

• Respiratory alkalosis:

• Acute resp. Alkalosis → $PCO_2 \downarrow$ = $HCO_3^- \downarrow$
10 mmHg 2 meq/L

• Chronic resp. Alkalosis → $PCO_2 \downarrow$ = $HCO_3^- \downarrow$
10 mmHg 4 meq/L

• Ex: pH = 7.25

Acidosis

$PCO_2 = 55$

Res. Acidosis

$HCO_3^- = 30$

met. Alkalosis

= Respiratory acidosis

$PCO_2 \uparrow = 55 - 40 = 15$

∴ For $10 \uparrow \rightarrow HCO_3^- \uparrow$ by 1

$15 \uparrow \rightarrow = 1.5$

∴ $HCO_3^- = 24 + 1.5 = 25.5$

∴ it is respiratory acidosis + metabolic alkalosis

Calculation of anion gap

• Serum anion gap = $Na^+ - (Cl^- + HCO_3^-)$

• Normal SAG = 8-12 meq/L

• metabolic acidosis → • Loss of HCO_3^-

• If loss of HCO_3^- compensated by Cl^-

• $Na^+ - (Cl^- \uparrow + HCO_3^- \downarrow)$

• Normal anion gap metabolic acidosis

- When loss of HCO_3^- is compensated by an ion other than Cl^- (unmeasured anion) $\rightarrow$ High anion gap metabolic acidosis
- In high anion gap metabolic acidosis calculate delta ratio

$$\begin{aligned}\text{Delta ratio} &= \frac{\text{Delta AG}}{\text{Delta HCO}_3^-} = \frac{\Delta \text{AG}}{\Delta \text{HCO}_3^-} \\ &= \frac{\text{AG} - 12}{24 - \text{HCO}_3^-}\end{aligned}$$

- Normal = 1-2 $\rightarrow$ High anion gap met.acidosis
- Delta ratio <1 $\rightarrow$ High anion gap + Normal anion gap
met. Acidosis met. Acidosis
- Delta ratio >2 $\rightarrow$ High anion gap + met. Alkalosis
met. Acidosis

ACID BASE REGULATION - 4

Urine anion gap

00:05:57

- To differentiate normal AG met. Acidosis due to RTA or GI loss, urine AG is done

$$\text{Urine AG} = \text{Urine Na}^+ + \text{urine K}^+ - \text{urine Cl}^-$$

- Positive urine AG $\rightarrow$ RTA
- Negative urine AG $\rightarrow$ GI loss of HCO_3^-

Example 7

- pH=7.24
- pCO₂=42
- pO₂=99
- Na=143 K=4 Cl=100 HCO₃=21

	pH	pCO ₂	pO ₂	HCO ₃ ⁻	AG	Delta ratio
Normal range	7.4	35 - 45 (40)	80 - 100 (90)	22 - 26 (24)	8 - 16 (12)	<1 - NAGMA+HAGMA 1-2 - HAGMA >2 - HAGMA+ met alkalosis

NAGMA - Normal Anion Gap metabolic Acidosis

HAGMA - High Anion Gap metabolic Acidosis

Answer

1. pH = 7.24 $\rightarrow$ pH < 7.4. - Acidosis
2. pCO₂ = 42 $\rightarrow$ > 40 - respiratory acidosis
3. HCO₃ = 21 $\rightarrow$ < 24 - metabolic acidosis

metabolic acidosis with respiratory acidosis

- For metabolic acidosis, always calculate AG
- Anion Gap = 143 - (100 + 21)
- = 22
- High anion gap metabolic acidosis
- Calculating delta ratio
- Delta ratio = $\frac{\text{AG} - 12}{24 - \text{HCO}_3^-}$
- = 10/3
- = >2

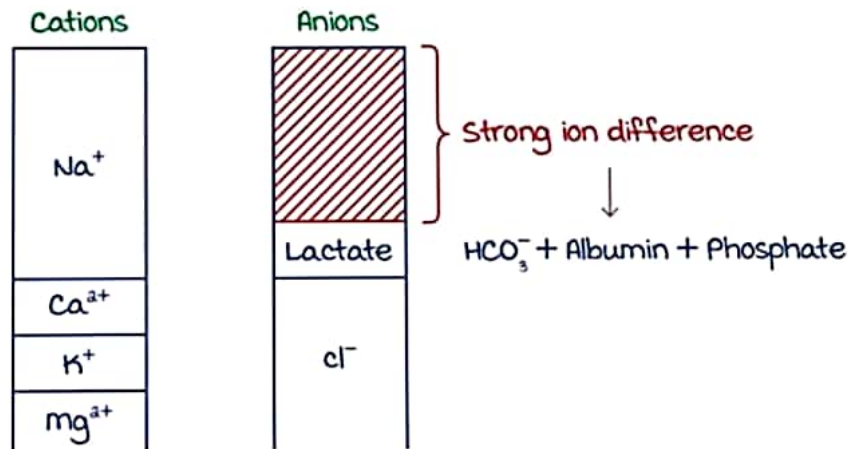
- Diagnosis = High anion gap metabolic acidosis + metabolic alkalosis + Respiratory acidosis

Strong ion difference

00:31:45

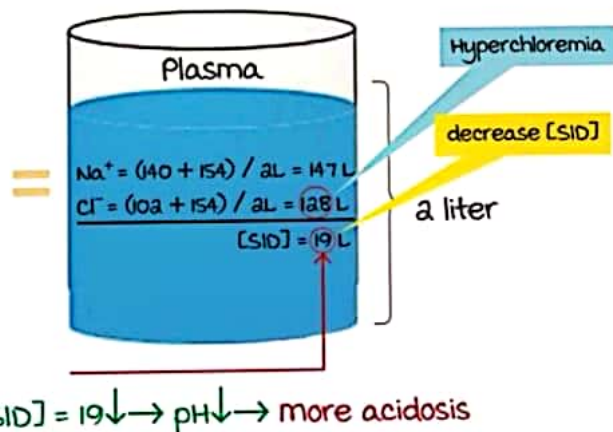
$$\text{Strong ion difference} = (\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+}) - (\text{Cl}^- + \text{Lactate}^-)$$

- Difference between measured strong cations & anions
- Normal SID $\rightarrow$ 40 meq/L



- $\text{SID} = \text{HCO}_3^- + \text{albumin} + \text{phosphate}$
- met. Alkalosis $\rightarrow$ SID $\uparrow$
- met. Acidosis $\rightarrow$ SID $\downarrow$
- Dehydration $\rightarrow$ SID $\uparrow$
- Lactic acidosis $\rightarrow$ SID $\downarrow$
- Hypoalbuminemia $\rightarrow$ SID $\downarrow$

Saline cause acidosis by decreasing [SID] due to the hyperchloremic



Osmolarity

00:47:56

- Calculated osmolarity = $2Na^+ + \frac{B. Glucose}{18} + \frac{BUN}{2.8} = 285-290$
- measured osmolarity → Osmometer
- Osmolal gap → • measured Osmolarity - calculated osmolarity > 10
 - methanol poisoning
 - Ethylene glycol poisoning
- Diagnosis = High anion gap metabolic acidosis + metabolic alkalosis + Respiratory acidosis